



PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

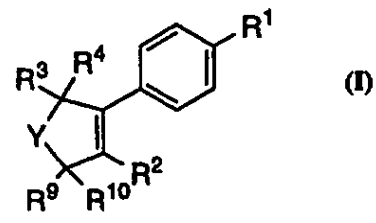
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 307/60, A61K 31/22, 31/38, 31/34, 31/365, 31/41, C07D 307/64, 405/04, 407/04, 409/04, 417/04, C07C 317/44		A1	(11) International Publication Number: WO 96/36623 (43) International Publication Date: 21 November 1996 (21.11.96)
(21) International Application Number: PCT/CA96/00306 (22) International Filing Date: 15 May 1996 (15.05.96) (30) Priority Data: 08/443,620 18 May 1995 (18.05.95) US (60) Parent Application or Grant (63) Related by Continuation US 08/443,620 (CIP) Filed on 18 May 1995 (18.05.95) (71) Applicant (for all designated States except US): MERCK FROSST CANADA INC. [CA/CA]; 16711 Trans Canada Highway, Kirkland, Quebec H9H 3L1 (CA). (72) Inventors; and (75) Inventors/Applicants (for US only): BLACK, Cameron [CA/CA]; 16711 Trans Canada Highway, Kirkland, Quebec H9H 3L1 (CA). GRIMM, Erich [DE/CA]; 16711 Trans Canada Highway, Kirkland, Quebec H9H 3L1 (CA). WANG, Zhaoyin [CA/CA]; 16711 Trans Canada Highway, Kirkland, Quebec H9H 3L1 (CA). LEGER, Serge [CA/CA];		16711 Trans Canada Highway, Kirkland, Quebec H9H 3L1 (CA). (74) Agent: MURPHY, Kevin, P.; Swabey Ogilvy Renault, Suite 1600, 1981 McGill College, Montreal, Quebec H3A 2Y3 (CA). (81) Designated States: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report.	

(54) Title: DIARYL-5-OXYGENATED-2-(5H)-FURANONES AS COX-2 INHIBITORS

(57) Abstract

The invention encompasses the novel compound of Formula (I) as well as a method of treating cyclooxygenase-2 mediated diseases comprising administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of Formula (I). The invention also encompasses certain pharmaceutical compositions for treatment of cyclooxygenase-2 mediated diseases comprising compounds of Formula (I).



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

- 1 -

TITLE OF THE INVENTION

DIARYL-5-OXYGENATED-2-(5H)-FURANONES AS COX-2
INHIBITORS

5 BACKGROUND OF THE INVENTION

This invention relates to methods of treating cyclooxygenase mediated diseases and certain pharmaceutical compositions therefor.

Non-steroidal, antiinflammatory drugs exert most of their
1 0 antiinflammatory, analgesic and antipyretic activity and inhibit
hormone-induced uterine contractions and certain types of cancer
growth through inhibition of prostaglandin G/H synthase, also known as
cyclooxygenase. Initially, only one form of cyclooxygenase was known,
this corresponding to cyclooxygenase-1 (COX-1) or the constitutive
1 5 enzyme, as originally identified in bovine seminal vesicles. More
recently the gene for a second inducible form of cyclooxygenase,
cyclooxygenase-2 (COX-2), has been cloned, sequenced and
characterized initially from chicken, murine and human sources. This
enzyme is distinct from the cyclooxygenase-1 which has been cloned,
2 0 sequenced and characterized from various sources including the sheep,
the mouse and man. The second form of cyclooxygenase,
cyclooxygenase-2, is rapidly and readily inducible by a number of
agents including mitogens, endotoxin, hormones, cytokines and growth
factors. As prostaglandins have both physiological and pathological
2 5 roles, we have concluded that the constitutive enzyme, cyclooxygenase-
1, is responsible, in large part, for endogenous basal release of
prostaglandins and hence is important in their physiological functions
such as the maintenance of gastrointestinal integrity and renal blood
flow. In contrast, we have concluded that the inducible form,
3 0 cyclooxygenase-2 (COX-2), is mainly responsible for the pathological
effects of prostaglandins where rapid induction of the enzyme would
occur in response to such agents as inflammatory agents, hormones,
growth factors, and cytokines. Thus, a selective inhibitor of
cyclooxygenase-2 will have similar antiinflammatory, antipyretic and

- 2 -

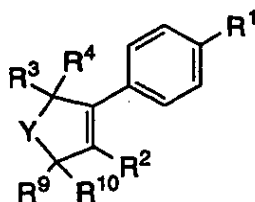
analgesic properties to a conventional non-steroidal antiinflammatory drug, and in addition would inhibit hormone-induced uterine contractions and have potential anti-cancer effects, but will have a diminished ability to induce some of the mechanism-based side effects.

- 5 In particular, such a compound should have a reduced potential for gastrointestinal toxicity, a reduced potential for renal side effects, a reduced effect on bleeding times and possibly a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects.

A brief description of the potential utilities of cyclooxygenase-2 inhibitors is given in an article by John Vane, Nature, Vol. 367, pp. 215-216, 1994 and in an article in Drug News and Perspectives, Vol. 7, pp. 501-512, 1994.

SUMMARY OF THE INVENTION

- 15 The invention encompasses the novel compound of Formula I as well as a method of treating cyclooxygenase-2 mediated diseases comprising administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of Formula I.



I

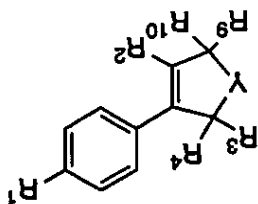
20 The invention also encompasses certain pharmaceutical compositions for treatment of cyclooxygenase-2 mediated diseases, comprising compounds of Formula I.

DETAILED DESCRIPTION OF THE INVENTION

- 25 The invention encompasses the novel compound of Formula I as well as a method of treating cyclooxygenase-2 mediated diseases comprising administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of Formula I.

30

- 3 -



I

or a pharmaceutically acceptable salt thereof

wherein:

5 Y is selected from the group consisting of

(a) C(R11)(R12),

(b) oxygen,

(c) sulfur,

R1 is selected from the group consisting of

10

(a) S(O)2CH3,

(b) S(O)2NH2,

(c) S(O)2NHC(O)CF3,

(d) S(O)(NH)NH2,

(e) S(O)(NH)NHC(O)CF3,

(f) S(O)2NHMe

(g) P(O)(CH3)NH2,

(h) P(O)(CH3)2,

(i) C(S)NH2

15

20 R2 is selected from the group consisting of

(a) C1-10alkyl,

(b) C3-10cycloalkyl,

(c) C2-10alkenyl

(d) C2-10alkynyl

(e) C3-10cycloalkenyl

(f) mono-, di-, tri- or tetra-substituted C3-C10cycloalkenyl

25

consisting of

(1) halo,

(2) C1-6alkoxy,

30

- 4 -

(g)	5	(3) C1-6alkylthio, (4) CN, (5) CF ₃ , (6) C1-10alkyl, (7) N ₃ , (8) -CO ₂ H, (9) -CO ₂ -C1-10alkyl, (10) -C(R ⁵)(R ⁶)-OH, (11) -C(R ⁵)(R ⁶)-O-C1-4alkyl, and (12) -C1-10alkyl-CO ₂ -R ⁵ ;
	10	(13) benzoyloxy, (14) -O-(C1-10alkyl)-CO ₂ R ⁵ , (15) -O-(C1-10alkyl)-NR ⁵ R ⁶ ,
(g)	15	unsubstituted or mono-, di- or tri-substituted phenyl or naphthyl wherein the substituent is selected from the group consisting of
	20	(1) C1-10alkyl, (2) C1-10alkoxy, (3) C1-10fluoroalkoxy, (4) C1-10alkylthio,
	25	(4) CN, (6) CF ₃ , (7) halo, (8) N ₃ , (9) -CO ₂ H, (10) -CO ₂ -C1-10alkyl,
	30	(11) -C(R ⁵)(R ⁶)-OH, (12) -C(R ⁵)(R ⁶)-O-C1-4alkyl, and (13) -C1-6alkyl-CO ₂ -R ⁵ ;
(h)		(14) benzoyloxy, (15) -O-(C1-10alkyl)-CO ₂ R ⁵ , (16) -O-(C1-10alkyl)-NR ⁵ R ⁶ ,

unsubstituted or mono-, di- or tri-substituted heteroaryl] wherein the heteroaryl is a monocyclic aromatic ring of 5

atoms, said ring having one hetero atom which is S, O, or N, and optionally 1, 2, or 3 additional N atoms; or the heteroaryl is a monocyclic ring of 6 atoms, said ring having one hetero atom which is N, and optionally 1, 2, 3, or 4 additional N atoms, said substituents being selected from the group consisting of	5	(1) C1-10alkyl, (2) C1-10alkoxy, (3) C1-10alkylthio, (4) CN, (5) CF ₃ , (6) halo, (7) N ₃ ,
	10	(1) C1-10alkyl, (2) C1-10alkoxy, (3) C1-10alkylthio, (4) CN, (5) CF ₃ , (6) halo, (7) N ₃ ,
	15	(8) -CO ₂ H, (9) -CO ₂ -C1-10alkyl, (10) -C(R ⁵)(R ⁶)-OH, (11) -C(R ⁵)(R ⁶)-O-C1-4alkyl, and (12) -C1-6alkyl-CO ₂ -R ⁵ ; (13) benzyloxy, (14) -O-(C1-10alkyl)-CO ₂ R ⁵ , (15) -O-(C1-10alkyl)-NR ⁵ R ⁶ ,
(i) an unsubstituted or a mono-, di-, tri- or tetra-substituted benzoheterocycle in which the heterocycle is a 5, 6, or 7-membered ring which may contain 1 or 2 heteroatoms chosen independently from O, S, or N and which may contain a carbonyl group or a sulfonyl group; the said substituents are selected from the group consisting of	20	(1) C1-10alkyl, (2) C1-10alkoxy, (3) C1-10alkylthio, (4) CN, (5) CF ₃ , (6) halo, (7) N ₃ ,
	25	
	30	

- 6 -

(j)	10	<p>a heterocycloalkyl group of 5, 6 or 7 members which contains 1 or 2 heteroatoms chosen from O, S, or N and optionally contains a carbonyl group or a sulfonyl group. an unsubstituted or a mono- or di- substituted benzocyclobutene in which the carbocycle is a 5, 6, or 7-membered ring which optionally contains a carbonyl group, the said substituents are selected from the group consisting of</p>	15
(k)	5	<p>(8) -CO₂H, (9) -CO₂-C₁₋₁₀alkyl, (10) -C(R⁵)(R⁶)-OH, (11) -C(R⁵)(R⁶)-O-C₁₋₄alkyl, and (12) -C₁₋₆alkyl-CO₂-R⁵; (13) benzyloxy, (14) -O-(C₁₋₁₀alkyl)-CO₂R⁵, (15) -O-(C₁₋₁₀alkyl)-NR⁵R⁶,</p>	5
	10	<p>(8) -CO₂H, (9) -CO₂-C₁₋₁₀alkyl, (10) -C(R⁵)(R⁶)-OH, (11) -C(R⁵)(R⁶)-O-C₁₋₄alkyl, and (12) -C₁₋₆alkyl-CO₂-R⁵; (13) benzyloxy, (14) -O-(C₁₋₁₀alkyl)-CO₂R⁵, (15) -O-(C₁₋₁₀alkyl)-NR⁵R⁶,</p>	15
	20	<p>(1) C₁₋₁₀alkyl, (2) C₁₋₁₀alkoxy, (3) C₁₋₁₀alkylthio, (4) CN, (5) CF₃, (6) halo, (7) N₃, (8) -CO₂H, (9) -CO₂-C₁₋₁₀alkyl,</p>	20
	25	<p>(10) -C(R⁵)(R⁶)-OH, (11) -C(R⁵)(R⁶)-O-C₁₋₄alkyl, and (12) -C₁₋₆alkyl-CO₂-R⁵; (13) benzyloxy, (14) -O-(C₁₋₁₀alkyl)-CO₂R⁵, (15) -O-(C₁₋₁₀alkyl)-NR⁵R⁶,</p>	30
	30	<p>R³ is hydrogen, C₁₋₁₀alkyl, CH₂OR⁷, CN, CH₂CN, or C_{1-fluoroalkyl}, F, CONR⁷₂, unsubstituted or mono- or di-substituted phenyl, unsubstituted or mono or di-substituted benzyl, unsubstituted or</p>	

- 7 -

mono- or di-substituted heteroaryl, unsubstituted or mono or di-substituted heteroaryl, wherein the substituents are selected from the group consisting of

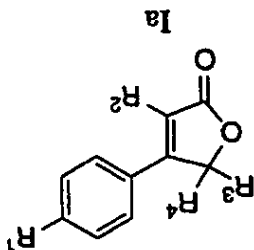
- | | | |
|------|---|----|
| (1) | C1-10alkyl, | 5 |
| (2) | C1-10alkoxy, | |
| (3) | C1-10alkylthio, | |
| (4) | CN, | |
| (5) | CF ₃ , | |
| (6) | halo, | |
| (7) | N ₃ , | 10 |
| (8) | -CO ₂ H, | |
| (9) | -CO ₂ -C1-10alkyl, | |
| (10) | -C(R ⁵)(R ⁶)-OH, | |
| (11) | -C(R ⁵)(R ⁶)-O-C1-4alkyl, and | |
| (12) | -C1-6alkyl-CO ₂ -R ⁵ ; | 15 |
| (13) | benzyloxy, | |
| (14) | -O-(C1-10alkyl)-CO ₂ R ⁵ , | |
| (15) | -O-(C1-10alkyl)-NR ⁵ R ⁶ , | |
| (a) | C1-10alkoxy, | 20 |
| (b) | C1-10alkylthio, | |
| (c) | C1-10fluoroalkoxy, | |
| (d) | -OH, | |
| (e) | -OCOR ⁷ , | 25 |
| (f) | -SH, | |
| (g) | -SCOR ⁷ , | |
| (h) | -OCO ₂ R ⁸ , | |
| (i) | -SCO ₂ R ⁸ , | |
| (j) | OCOR ⁷ ₂ , and | |
| (k) | SCONR ⁷ ₂ ; | 30 |
| (l) | C3-10cycloalkoxy, | |
| (m) | C3-10cycloalkylthio; | |
| (n) | -NR ⁷ ₂ ; | |

each R⁵ or R⁶ is independently selected from the group consisting of

R⁴ is

5	each R ⁷ is independently selected from the group consisting of (a) hydrogen and R ⁸ ; (b) R ⁸ ; atoms; form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7	
10	each R ⁸ is independently selected from the group consisting of (a) C ₁₋₁₀ alkyl, (b) phenyl or monosubstituted phenyl wherein the substituents may be halo, C ₁₋₁₀ alkoxy, C ₁₋₁₀ alkylthio, CN, or CF ₃ , (c) benzyl or monosubstituted benzyl wherein the substituents may be halo, C ₁₋₁₀ alkoxy, C ₁₋₁₀ alkyl, C ₁₋₁₀ alkylthio, CN, or CF ₃ , and C ₃₋₁₀ cycloalkyl	
15	R ⁹ and R ¹⁰ are independently selected from the group consisting of: (a) hydrogen, (b) C ₁₋₁₀ alkyl, (c) C ₃₋₁₀ cycloalkyl, or R ⁹ and R ¹⁰ together form a double bonded O or S;	
20	R ¹¹ and R ¹² are independently selected from the group consisting of: (a) hydrogen, (b) unsubstituted or mono- or di-substituted phenyl or unsubstituted or mono- or di-substituted benzyl or unsubstituted or mono- or di-substituted heteroaryl, or unsubstituted or mono- or di-substituted heteroarylthio, or said substituents being selected from the group consisting of: (1) C ₁₋₁₀ alkyl, (2) C ₁₋₁₀ alkoxy, (3) C ₁₋₁₀ alkylthio, (4) CN,	
25		
30		

- (5) CF₃,
 (6) halo,
 (7) N₃,
 (8) -CO₂H,
 (9) -CO₂-C₁₋₁₀alkyl,
 (10) -C(R⁵)(R⁶)-OH,
 (11) -C(R⁵)(R⁶)-O-C₁₋₄alkyl, and
 (12) -C₁₋₆alkyl-CO₂-R⁵;
 (13) benzyloxy,
 (14) -O-(C₁₋₁₀alkyl)-CO₂R⁵,
 (15) -O-(C₁₋₁₀alkyl)-NR⁵R⁶,
 (c) C₁₋₁₀alkyl, CH₂OR⁷, CN, CH₂CN, C₁₋₁₀fluoroalkyl, F or
 CONR⁷₂; or
 R¹¹ and R¹² together with the carbon to which they are attached
 form a carbonyl or a saturated monocyclic carbon ring of
 3, 4, 5, 6 or 7 atoms;
 R¹³ and R¹⁴ are independently selected from the group consisting of:
 (a) hydrogen,
 (b) C₁₋₁₀alkyl, or
 R¹³ and R¹⁴ together with the carbon to which they are attached
 form a carbonyl, -C(=S)-, or a saturated monocyclic carbon
 ring of 3, 4, 5, 6, or 7 atoms.
- 2 5 formula
- 3 0 wherein:
 R¹ is selected from the group consisting of
 (a) S(O)₂CH₃,



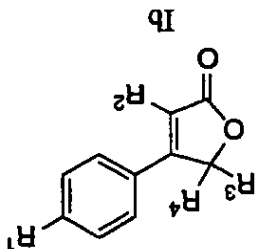
- 10 -

5	R ² is selected from the group consisting of	(b) S(O)NH ₂ , (c) S(O)NHC(O)CF ₃ , (d) S(O)(NH)NH ₂ ;
10	unsubstituted or mono-, di- or tri-substituted phenyl wherein the substituent is selected from the group consisting of	(1) halo, (2) C ₁ -alkoxy, (3) C ₁ -alkylthio, (4) CN, (5) CF ₃ , (6) C ₁ -alkyl, (7) N ₃ , (8) -C(R ⁵)(R ⁶)-OH,
15	R ³ is hydrogen, C ₁ -alkyl, CH ₂ OR ⁷ , CN, CH ₂ CN, or C ₁ -fluoroalkyl, F, CONR ⁷ ₂ ;	R ⁴ is
20	(a) C ₁ -alkoxy, (b) C ₁ -alkylthio,	(c) -OH, (d) -OCOR ⁷ , (e) -SH, (f) -SCOR ⁷ , (g) -OCO ₂ R ⁸ , (h) -SCO ₂ R ⁸ , (i) OCONR ⁷ ₂ , and (j) SCONR ⁷ ₂ ;
25	each R ⁵ or R ⁶ is independently selected from the group consisting of	(a) hydrogen, and (b) C ₁ -alkyl,
35	each R ⁷ is independently selected from the group consisting of	(a) hydrogen and (b) R ⁸ ;

- 11 -

- each R⁸ is independently selected from the group consisting of
- (a) C1-4alkyl,
 - (b) phenyl or monosubstituted phenyl wherein the substituents may be halo, C1-4alkyl, C1-4alkoxy, C1-4alkylthio, CN, or CF₃;
 - (c) benzyl or monosubstituted benzyl wherein the substituents may be halo, C1-4alkyl, C1-4alkoxy, C1-4alkylthio, CN, or CF₃. and

10 Within this genus are the compounds of formula Ib



wherein:

R¹ is selected from the group consisting of

- (a) S(O)₂CH₃,
- (b) S(O)₂NH₂,

R² is selected from the group consisting of

unsubstituted or mono-, di- or tri-substituted phenyl wherein the substituent is selected from the group

consisting of

- (1) halo,
- (2) C1-3alkoxy,
- (3) CF₃,
- (4) C1-3alkyl,

R³ is hydrogen, C1-3alkyl, CH₂OR⁷, C1-4fluoroalkyl;

R⁴ is

- (a) C1-3alkoxy,
- (b) C1-3alkylthio,
- (c) -OH,
- (d) -OCOR⁷,

30

- 12 -

(e) -SCOR₇,
 (f) OCONR₇, and
 (g) SCONR₇;
 each R₇ is independently selected from the group consisting of

5 (a) hydrogen and
 (b) R₈;

each R₈ is C₁₋₃alkyl.

10 For purposes of this specification heteroaryl as in R₂ is
 intended to include, but is not limited to optionally mono- or di-

substituted

(1) furyl,

(2)

diazinyl, triazinyl, tetrazinyl,

(3)

imidazolyl,

(4)

isooxazolyl,

(5)

isothiazolyl,

(6)

oxadiazolyl,

(7)

oxazolyl,

(8)

pyrazolyl,

(9)

pyrrolyl,

(10)

thiadiazolyl,

(11)

thiazolyl,

(12)

thienyl,

(13)

triazolyl, or

(14)

tetrazolyl.

1 5

2 0

2 5

Similarly, for purposes of this specification cyclic groups
 such as a heterocycloalkyl or benzocarbocycle or benzoheterocycle such
 as in R₂ is intended to include, but is not limited to optionally mono- or

3 0 di-substituted

(1) indolyl,

(2) benzofuranyl,

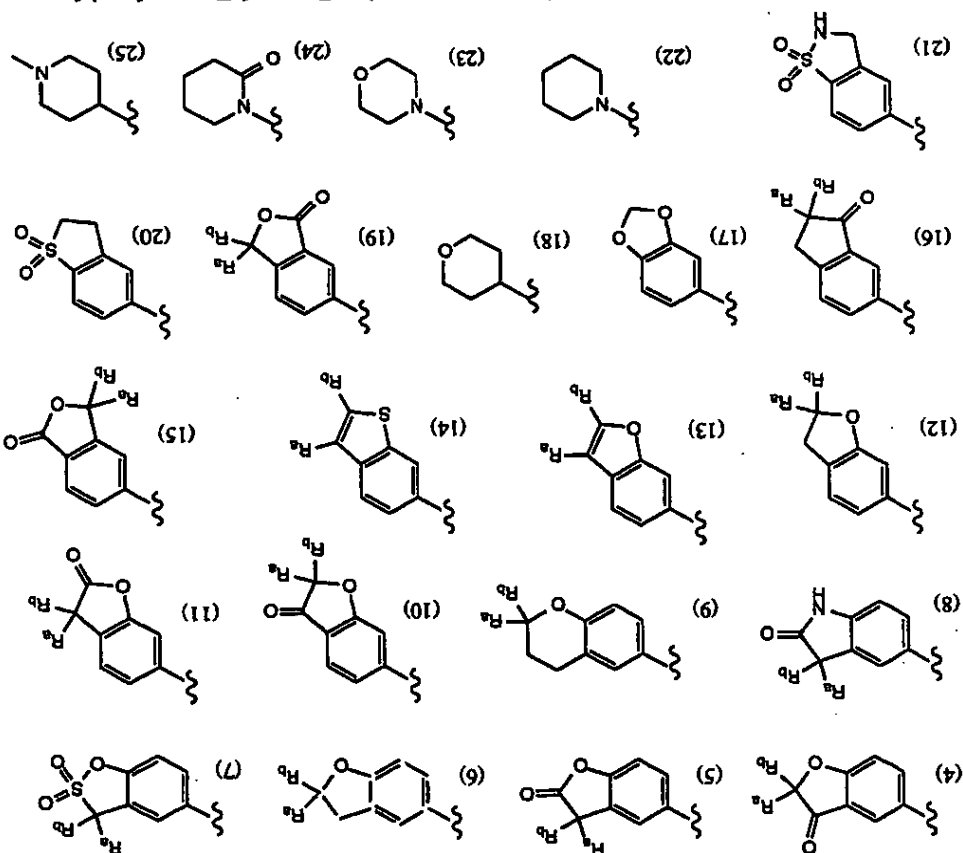
(3) benzothienyl,

in which the substituents comprise R_a and R_b and said substituents are selected from hydrogen, halo, -OH, CF₃, C1-3alkoxy, C1-3alkylthio, and C1-3alkyl.

One genus of compounds of formula I is that in which R⁹ and R¹⁰ form a double-bonded O, and Y is O.

For purposes of this specification, alkyl is defined to include linear and branched structures of the indicated number of carbon atoms, including, but not restricted to, methyl, ethyl, propyl, -isopropyl, n-, i-, s- and t-butyl, pentyl, hexyl, 1,1-dimethylethyl, and decyl.

Cycloalkyl means an alkyl group of the indicated number of carbon atoms containing one or more rings anywhere in the structure; examples of cycloalkyl are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 2-norbornyl, 1-adamantyl and the like.



Fluoroalkyl includes alkyl groups of the indicated number of carbon atoms of a straight or branched configuration, in which one or more hydrogen is replaced by fluorine. Examples are -CH₂F, -CHF₂, -CF₃, -CH₂CF₃, n-C₉H₁₈CF₃, -CH(CF₃)₂, and the like.

Cyclofluoroalkyl includes fluoroalkyl groups of the indicated number of carbon atoms, containing one or more rings anywhere in the structure, in which one or more hydrogen is replaced by fluorine. Examples are c-pr-F₅, c-hex-F₁₁, and the like.

Alkenyl means linear and branched alkenyl groups of the indicated number of carbon atoms. Examples of alkenyl groups are allyl, 5-decen-1-yl, 2-dodecen-1-yl, 2-ethyl-1-buten-1-yl, and the like.

Cycloalkenyl means alkenyl groups of the indicated number of carbon atoms, containing one or more rings anywhere in the structure, and in which the alkenyl double bond may be located anywhere in the structure. Examples of cycloalkenyl groups are cyclopropen-1-yl, cyclohexen-3-yl, 2-vinyladamant-1-yl, 5-methylenedodec-1-yl, and the like.

Alkyl means linear and branched alkyl groups of the indicated number of carbon atoms. Examples of alkyl groups are ethynyl, 2-pentadecyn-1-yl, 1-eicosyn-1-yl, and the like.

Cycloalkynyl means alkynyl groups of 5 or more carbon atoms, which include a ring. The alkynyl triple bond may be located anywhere in the group, with the proviso that if it is within a ring, such a ring must be 10 members or greater. Examples of cycloalkynyl are cycloiododecyn-3-yl, 3-cyclohexyl-1-propyn-1-yl, and the like.

Similarly, alkoxyl is intended to include alkoxyl groups of the indicated number of carbon atoms of a straight or branched configuration. Examples of alkoxyl groups include methoxyl, ethoxyl, propoxyl, isopropoxyl, and the like.

Cycloalkoxyl means an alkoxyl group of the indicated number of carbon atoms containing one or more rings anywhere in the structure; examples of cycloalkoxyl are cyclopropoxyl, 2-cyclopropylmethoxyl, cyclobutoxyl, cyclopentoxyl, cyclohexoxyl, 2-norbornoxyl, 1-adamantoxyl, and the like.

3 0

5

1 0

1 5

2 0

2 5

3 0

Likewise, alkylthio is intended to include alkylthio groups of the indicated number of carbon atoms of a straight or branched configuration. Examples of alkylthio groups include methylthio, n-propylthio, isopropylthio, decylthio, etc. By way of illustration, the n-propylthio group signifies $\text{-SCH}_2\text{CH}_2\text{CH}_3$.

Cycloalkylthio means an alkylthio group of the indicated number of carbon atoms containing one or more rings anywhere in the structure; examples of cycloalkylthio are cyclopropylthio, cyclopentylthio, cyclohexylthio, 2-norbornylthio, 1-adamantylthio, and the like.

Fluoroalkoxy includes alkoxy groups of the indicated number of carbon atoms of a straight or branched configuration, in which one or more hydrogen is replaced by fluorine. Examples are $\text{-OCH}_2\text{F}$, -OCHF_2 , -OCF_3 , $\text{-OCH}_2\text{CF}_3$, $\text{-O-n-C}_9\text{H}_{18}\text{CF}_3$, $\text{-OCH}(\text{CF}_3)_2$ and the like.

Cyclofluoroalkoxy means an alkoxy group of the indicated number of carbon atoms containing one or more rings anywhere in the structure, and in which one or more hydrogen is replaced by fluorine; examples of cyclofluoroalkoxy are $\text{-C}_3\text{F}_5\text{O-}$, $\text{-C}_3\text{F}_5\text{CH}_2\text{O-}$, $\text{C}_6\text{F}_{11}\text{O}$, and the like.

Fluoroalkylthio includes alkylthio groups of the indicated number of carbon atoms of a straight or branched configuration, in which one or more hydrogen is replaced by fluorine. Examples are $\text{-SCH}_2\text{F}$, -SCHF_2 , -SCF_3 , $\text{-SCH}_2\text{CF}_3$, $\text{-S-n-C}_9\text{H}_{18}\text{CF}_3$, $\text{-SCH}(\text{CF}_3)_2$ and the like.

Cyclofluoroalkylthio means an alkylthio group of the indicated number of carbon atoms containing one or more rings anywhere in the structure, and in which one or more hydrogen is replaced by fluorine; examples of cyclofluoroalkylthio are $\text{-C}_3\text{F}_5\text{S-}$, $\text{-C}_3\text{F}_5\text{SCH}_2\text{S-}$, $\text{C}_6\text{F}_{11}\text{S}$, and the like. Halo includes F, Cl, Br, or I. Heteroaryl includes furan, thiophene, pyrrole, isoxazole, isothiazole, pyrazole, oxazole, thiazole, imidazole, 1,2,3-oxadiazole, 1,2,3-thiadiazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,2,3-triazole, 1,2,3-triazole, 1,2,3-triazole, 1,2,5-oxadiazole, 1,2,5-thiadiazole, pyridine, pyridazine,

pyrimidine, pyrazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,4,5-tetrazine, and the like. The term aryl refers to both all-carbon (e.g. benzene, naphthalene) or heteroaryl aromatic rings.

As will be appreciated by those of skill in the art, when a substituent (e.g. alkyl, aryl, R¹ through R¹⁴, etc.) occurs more than one time in a variable or in formula I, its definition at one occurrence is independent of its definition at every other occurrence. For example, in CONR⁷2, the two R⁷'s need not be simultaneously the same, although each selection must be consistent with the markush group defining R⁷.

Exemplifying the invention are:

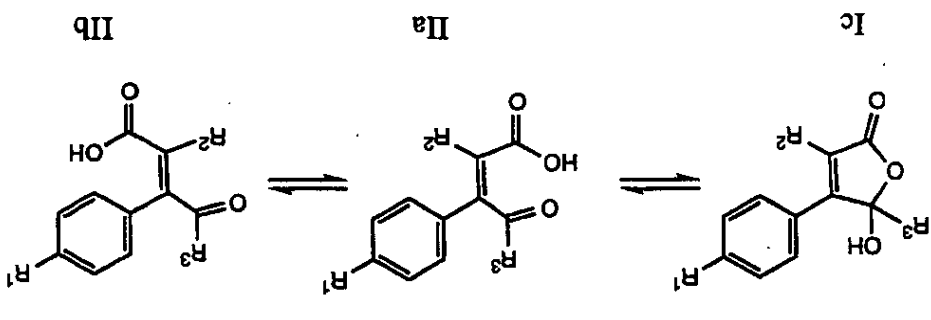
- (1) Benzoic acid, 3-(4-(methylsulfonyl)phenyl)-5-oxo-4-phenyl-2,5-dihydrofuran-2-yl ester,
- (2) 5-Hydroxy-4-(4-(methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone,
- (3) 5-Hydroxy-3-(3,4-difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,
- (4) 5-Hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone,
- (5) 3-(4-Fluorophenyl)-5-hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,
- (6) 3-(4-Chlorophenyl)-5-hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,
- (7) 3-(3,4-Difluorophenyl)-5-hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,
- (8) 3-(3-Fluorophenyl)-5-hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,
- (9) 3-(3,5-Difluorophenyl)-5-hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,
- (10) 5-Methoxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone,
- (11) 3-(4-Chlorophenyl)-5-methoxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,
- (12) 3-(3,4-Difluorophenyl)-5-methoxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,

5	(13) 3-(3-Fluorophenyl)-5-methoxy-5-methyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone, (14) 3-(3,5-Difluorophenyl)-5-methoxy-5-methyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone, (15) 3-(4-Fluorophenyl)-5-methoxy-5-methyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone, (16) 5-Ethoxy-3-(4-Fluorophenyl)-5-methyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone, (17) 3-(4-Fluorophenyl)-5-methyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone, (18) 3-(4-Fluorophenyl)-5-isopropoxy-5-methyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone, (19) 5-Methyl-5-methylthio-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone, (20) 5-Ethylthio-5-methyl-4-(4-methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone, (21) 5-Ethyl-5-hydroxy-4-(4-methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone, (22) 5-Ethyl-3-(3-Fluorophenyl)-5-hydroxy-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone, (23) Acetic acid, 3-(4-(methylsulfonyl)phenyl)-2-methyl-5-oxo-4-phenyl-2,5-dihydrofuran-2-yl ester (24) 5-Hydroxy-5-methyl-4-(4-methylsulfonyl)phenyl)-3-(2-naphthyl)-2-(5H)-furanone, (25) Sodium 2-(4-Fluorophenyl)-3-((4-methylsulfonyl)phenyl)-4-oxo-2-pentenoate, and (26) Sodium 2-(4-chlorophenyl)-3-((4-methylsulfonyl)phenyl)-4-oxo-2-pentenoate.
10	
15	
20	
25	
30	

Some of the compounds of Formula I of the present invention in which $R^4 = OH$ may exist in a tautomeric open chain keto-acid form of Formula IIa or IIb below, depending on the substituents at R^1 , R^2 , or R^3 or the pH. In such cases, the rate of equilibration may vary, and activity may reside with either tautomer. In particular, it may

- 18 -

be possible to form a salt of compound Ic with a base, said salt existing predominantly in the tautomeric form IIa. Thus, structures IIa and IIb are within the scope of Formula I.



10 Some of the compounds described herein contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention is meant to comprehend such possible diastereomers as well as their racemic and resolved, enantiomerically pure forms and pharmaceutically acceptable salts thereof.

15 Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

20 In a second embodiment, the invention encompasses pharmaceutical compositions for inhibiting cyclooxygenase and for treating cyclooxygenase mediated diseases as disclosed herein comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of formula I as described above.

25 Within this embodiment the invention encompasses pharmaceutical compositions for inhibiting COX-2 and for treating COX-2 mediated diseases as disclosed herein comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of formula I as described above.

In a third embodiment, the invention encompasses a method of inhibiting cyclooxygenase and treating cyclooxygenase mediated diseases, advantageously treated by an active agent that selectively inhibits COX-2 in preference to COX-1 as disclosed herein comprising: administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of Formula I as disclosed herein.

The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a pharmaceutical salt, thereof, and may also contain a pharmaceutical carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganese, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, diethylenediamine, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, adipic, aspartic, 1,5-naphthalenedisulfonic, benzenesulfonic, benzoic, camphorsulfonic, citric, 1,2-ethanedithiolonic, ethanesulfonic,

ethylenediaminetetraacetic, fumaric, glucosheptonic, gluconic, glutamic, hydriodic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, 2-naphthalenesulfonic, nitric, oxalic, pantoic, pantothenic, phosphoric, pivalic, propionic, salicylic, stearic, succinic, sulfuric, tartaric, p-toluenesulfonic acid, undecanoic, 10-undecenoic, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, methanesulfonic, phosphoric, sulfuric and tartaric acids.

It will be understood that in the discussion of methods of treatment which follows, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

The Compound of Formula I is useful for the relief of pain, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns, injuries, following surgical and dental procedures. In addition, such a compound may inhibit cellular neoplastic transformations and metastatic tumor growth and hence can be used in the treatment of cancer.

Compound I may also be of use in the treatment and/or prevention of cyclooxygenase-mediated proliferative disorders such as may occur in diabetic retinopathy and tumour angiogenesis.

Compound I will also inhibit prostanoind-induced smooth muscle contraction by preventing the synthesis of contractile prostanoids and hence may be of use in the treatment of dysmenorrhea, premature labor, asthma and eosinophil related disorders. It will also be of use in the treatment of Alzheimer's disease, and for the prevention of bone loss (treatment of osteoporosis).

By virtue of its high COX-2 inhibitory activity and/or its specificity for COX-2 over COX-1, Compound I will prove useful as an alternative to conventional non-steroidal antiinflammatory drugs (NSAID'S) particularly where such non-steroidal antiinflammatory

5 drugs may be contra-indicated such as in patients with peptic ulcers, recurrent history of gastrointestinal lesions; GI bleeding, coagulation disorders including anemia such as hypoprothrombinemia, haemophilia or other bleeding problems; kidney disease; those prior to surgery or taking anticoagulants.

Similarly, Compound I, will be useful as a partial or

complete substitute for conventional NSAID'S in preparations wherein they are presently co-administered with other agents or ingredients.

1 0 Thus in further aspects, the invention encompasses pharmaceutical

compositions for treating COX-2 mediated diseases as defined above

comprising a non-toxic therapeutically effective amount of the

compound of Formula I as defined above and one or more ingredients such as another pain reliever including acetaminophen or phenacetin; a

1 5 potentiator including caffeine; an H₂-antagonist, aluminum or

magnesium hydroxide, simethicone, a decongestant including

phenylephrine, phenylpropanolamine, pseudophedrine, oxymentazoline,

ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-

desoxyephedrine; an antitussive including codeine, hydrocodone,

2 0 caramiphen, carbapentane, or dexamethorphan; a diuretic; a sedating

or non-sedating antihistamine. In addition the invention encompasses a

method of treating cyclooxygenase mediated diseases comprising:

administration to a patient in need of such treatment a non-toxic

therapeutically effect amount of the compound of Formula I, optionally

2 5 co-administered with one or more of such ingredients as listed

immediately above.

For the treatment of any of these cyclooxygenase mediated

diseases Compound I may be administered orally, topically,

parenterally, by inhalation spray or rectally in dosage unit formulations

3 0 containing conventional non-toxic pharmaceutically acceptable carriers,

adjuvants and vehicles. The term parenteral as used herein includes

subcutaneous injections, intravenous, intramuscular, intrasternal

injection or infusion techniques. In addition to the treatment of warm-

blooded animals such as mice, rats, horses, cattle sheep, dogs, cats, etc., the compound of the invention is effective in the treatment of humans. As indicated above, pharmaceutical compositions for treating COX-2 mediated diseases as defined may optionally include one or more ingredients as listed above.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the technique described in the U.S. Patent 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients is mixed

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients is mixed

- with water or miscible solvents such as propylene glycol, PEGs and ethanol, or an oil medium, for example peanut oil, liquid paraffin, or olive oil.
- 5 Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethacrylate, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphate, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monoolate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monoolate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.
- 15 Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example, arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example, beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.
- 30 Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting
- 25 active ingredient in a vegetable oil, for example, arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example, beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example, olive oil or arachis oil, or a mineral oil, for example, liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example, soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan monoolate, and condensation products of the said partial esters with ethylene oxide, for example, polyoxy-ethylene sorbitan monoolate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example, glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. Cosolvents such as ethanol, propylene glycol or polyethylene glycols may also be used. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compound I may also be administered in the form of a suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating

excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, gels, solutions or suspensions, etc., containing the compound of Formula I are employed. (For purposes of this application, topical application shall include mouth washes and gargles.) Topical formulations may generally be comprised of a pharmaceutical carrier, cosolvent, emulsifier, penetration enhancer, preservative system, and emollient.

10 Dosage levels of the order of from about 0.01 mg to about 140 mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5 mg to about 7 g per patient per day. For example, inflammation may be effectively treated by the administration of from about 0.01 to 50 mg of the compound per kilogram of body weight per day, or alternatively about 0.5 mg to about 3.5 g per patient per day.

15 The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 0.5 mg to 5 g of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, or 1000 mg.

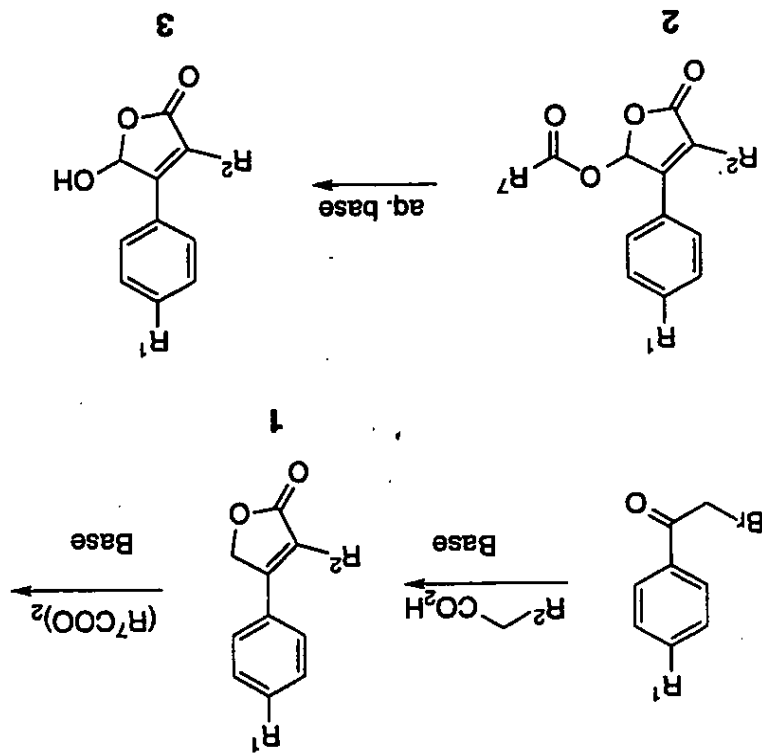
25 It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

30

The compounds of the present invention can be prepared according to the following methods.

Method A

An appropriately substituted aryl bromomethyl ketone is reacted with an appropriately substituted aryl acetic acid in a solvent such as acetonitrile in the presence of a base such as triethylamine and then treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to afford lactone 1. Further treatment of 1 with DBU, followed by $(R^7COO)_2$, provides ester 2, which can then be hydrolyzed with aqueous base to give hemiacetal 3.

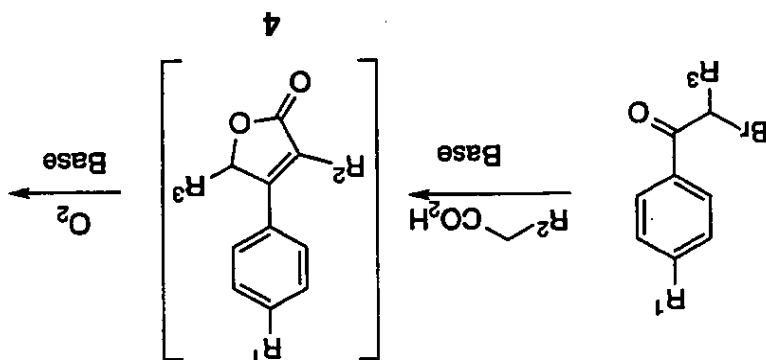


Method B

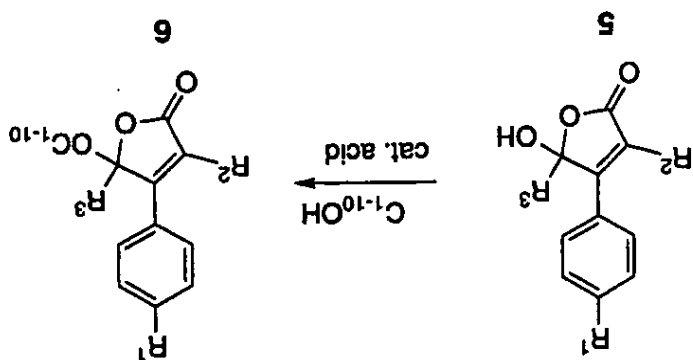
An appropriately substituted aryl bromomethyl ketone is reacted with an appropriately substituted aryl acetic acid in a solvent such as

- 27 -

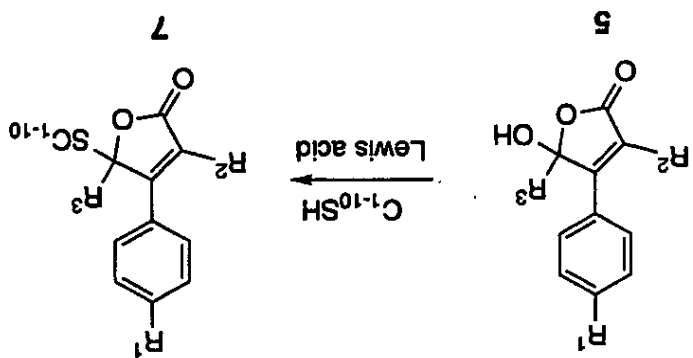
acetonitrile in the presence of a base such as triethylamine and then treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to afford lactone **4** and the crude reaction mixture can then be exposed to excess oxygen until **4** is completely oxidized to hemiketal **5**.

**Method C**

Hemiketal **5** is heated in an appropriate alcohol in the presence of a catalytic amount of acid such as H₂SO₄ to afford ketal **6**.

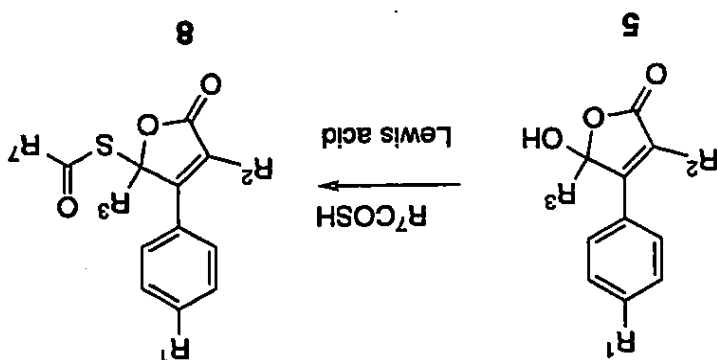


Method D
Hemiketal 5 is treated with an appropriate thiol in the presence of a Lewis acid such as Et₂O·BF₃ to afford thioacetal 7.

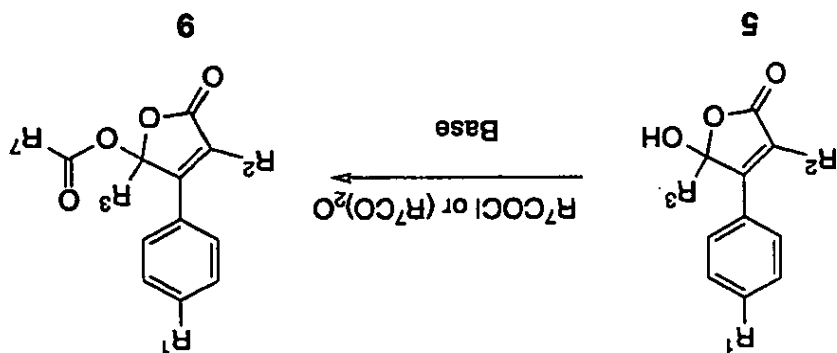


Method E
Hemiketal 5 is treated with an appropriate thio acid in the presence of a Lewis acid such as Et₂O·BF₃ to afford thioacetal 8.

- 29 -



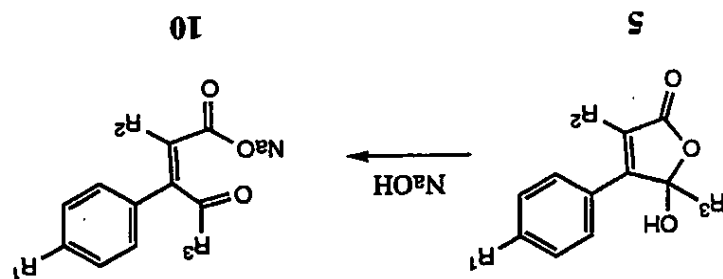
Method F
Hemiketal 5 is treated with an appropriate acid chloride or anhydride in the presence of a base to afford ketal 9

**METHOD G**

Hemiketal 5 is suspended in EtOH and treated with one equivalent of NaOH. The solvent is evaporated, and the salt is dissolved in water and freeze-dried to provide keto-carboxylate 10.

10

- 30 -



Compounds 2, 3, 5, 6, 7, 8, 9 and 10 are representatives of
5 structures of the present invention.

Tables I illustrates novel compounds of the present invention.

Table I

Example	Method	Chemical Structure
1	A	
2	A	
3	A	
4	B	
5	B	

Table I (continued)

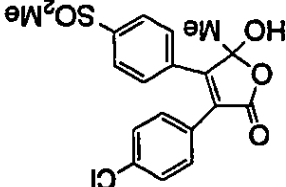
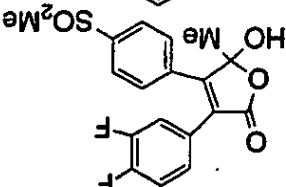
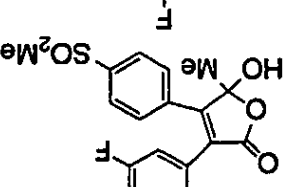
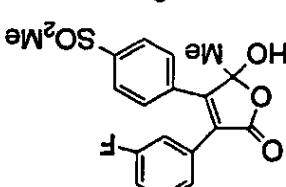
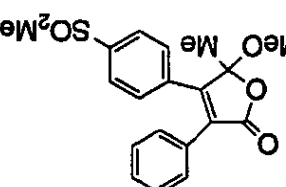
Example	Method		
6	B		
7	B		
8	B		
9	B		
10	C		

Table I (continued)

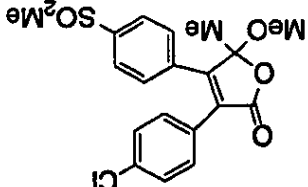
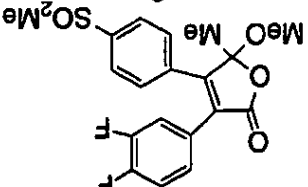
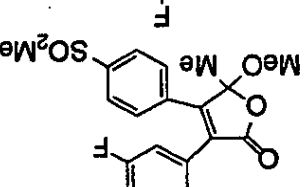
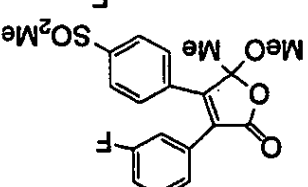
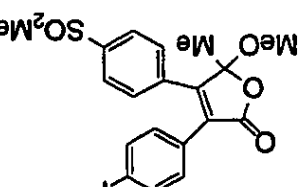
Example	Method	
11	C	
12	C	
13	C	
14	C	
15	C	

Table I (continued)

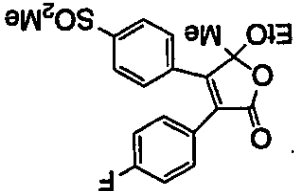
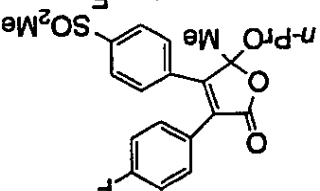
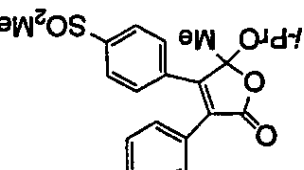
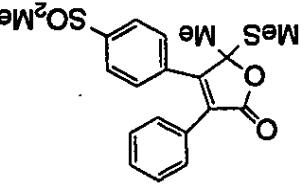
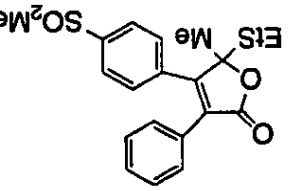
Example	Method	
16	C	
17	C	
18	C	
19	D	
20	D	

Table I (continued)

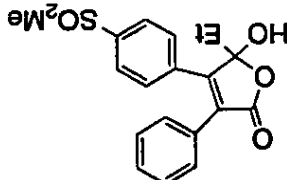
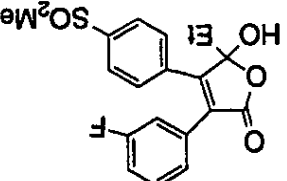
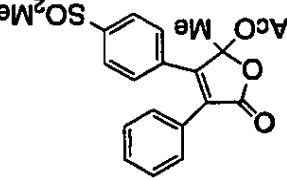
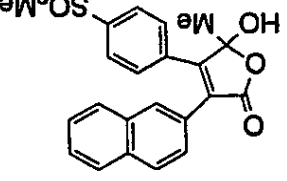
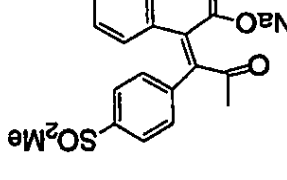
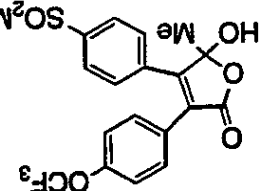
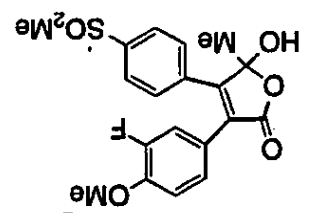
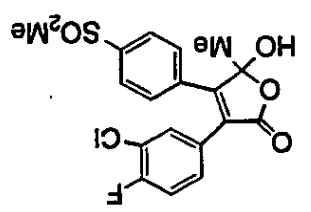
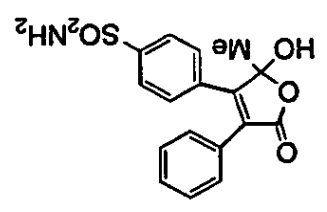
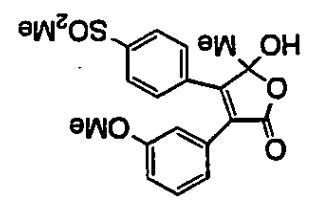
Example	Method	
21	B	
22	B	
23	F	
24	B	
25	G	

Table I (continued)

Example	Method	
26	B	
27	B	
28	B	
29	B	
30	B	

Table I (continued)

Example	Method	
31	B	
32	B	
33	B	
34	B	
35	B	

- 38 -

Table I (continued)

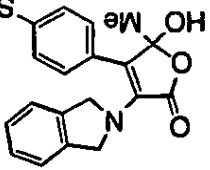
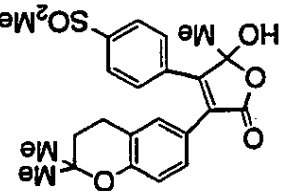
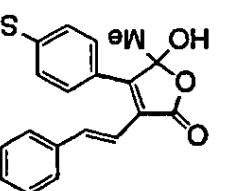
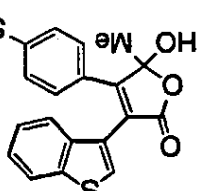
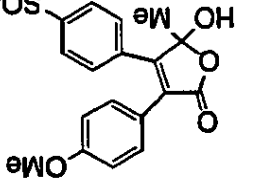
Example	Method	
36	B	
37	B	
38	B	
39	B	
40	B	

Table I (continued)

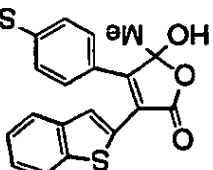
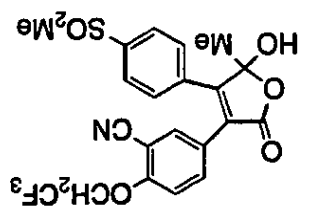
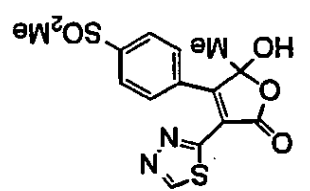
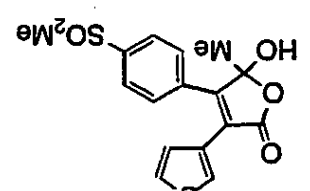
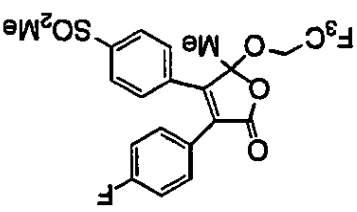
Example	Method	
41	B	
42	B	
43	B	
44	B	
45	C	

Table I (continued)

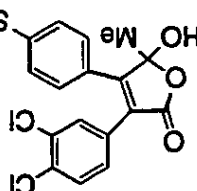
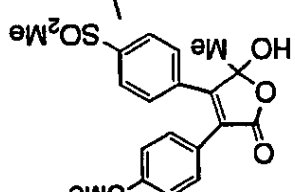
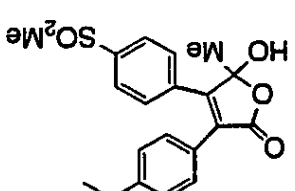
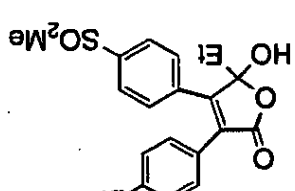
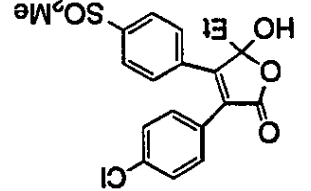
Example	Method	
46	B	
47	B	
48	B	
49	B	
50	B	

Table I (continued)

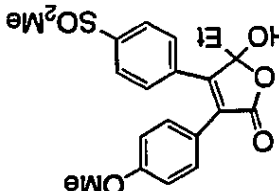
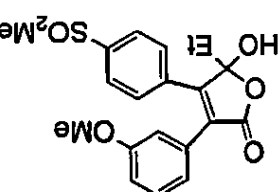
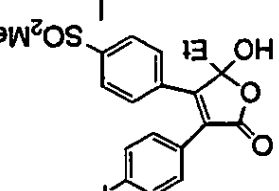
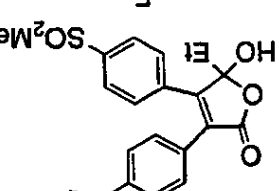
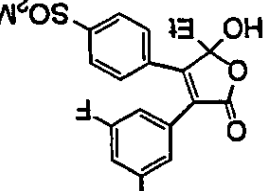
Example	Method	
51	B	
52	B	
53	B	
54	B	
55	B	

Table I (continued)

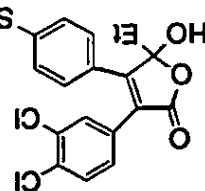
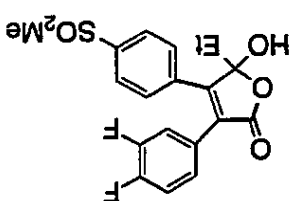
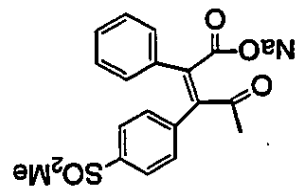
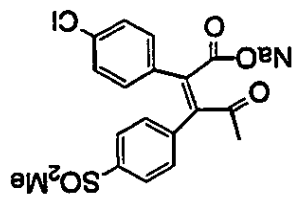
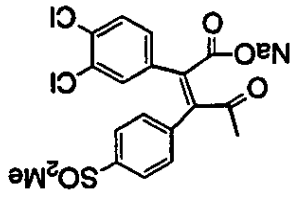
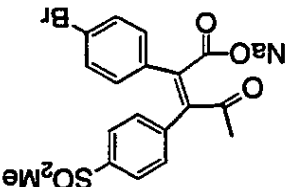
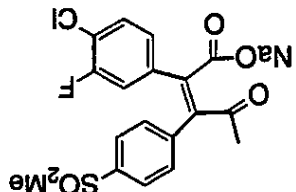
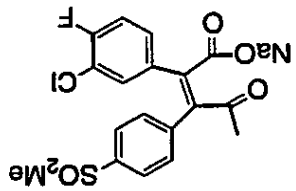
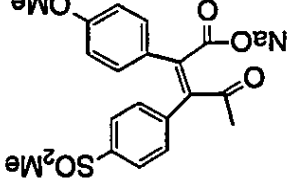
Example	Method	
56	B	
57	B	
58	G	
59	G	
60	G	

Table I (continued)

Example	Method	
61	G	
62	G	
63	G	
64	G	

Assays for determining Biological Activity

The compound of Formula I can be tested using the following assays to determine their cyclooxygenase-2 inhibiting activity.

Inhibition of Cyclooxygenase Activity

Compounds were tested as inhibitors of cyclooxygenase activity in whole cell cyclooxygenase assays. Both of these assays measured prostaglandin E₂ synthesis in response to A.A., using a radioimmunoassay. Cells used for these assays were human osteosarcoma 143 cells (which specifically express COX-2) and human

U-937 cells (which specifically express COX-1). In these assays, 100% activity is defined as the difference between prostaglandin E2 synthesis in the absence and presence of arachidonate.

5 Assay

For cyclooxygenase assays, osteosarcoma cells are cultured in 1 mL of media in 24-well multidishes (Nunc) until confluent (1-2 x 10⁵ cells/well). U-937 cells are grown in spinner flasks and resuspended to a final density of 1.5 x 10⁶ cells/mL in 24-well multidishes (Nunc). Following washing and resuspension of osteosarcoma and U-937 cells in 1 mL of HBSS, 1 µL of a DMSO solution of test compound or DMSO vehicle is added, and samples gently mixed. All assays are performed in triplicate. Samples are then incubated for 5 or 15 minutes at 37°C, prior to the addition of A.A. A.A. (peroxide-free, Cayman Chemical) is prepared as a 10 mM stock solution in ethanol and further diluted 10-fold in HBSS. An aliquot of 10 µL of this diluted solution is added to the cells to give a final A.A. concentration of 10 µM. Control samples are incubated with ethanol vehicle instead of A.A. Samples are again gently mixed and incubated for a further 10 min at 37°C. For osteosarcoma cells, reactions are then stopped by the addition of 100 µL of 1N HCl with mixing and by the rapid removal of the solution from cell monolayers. For U-937 cells, reactions are stopped by the addition of 100 µL of 1N HCl with mixing.

Samples are then neutralized by the addition of 100 µL of 1N NaOH and PGE2 levels measured by radioimmunoassay.

Rat Paw Edema Assay - Protocol

Male Sprague-Dawley rats (150 - 200 g) were fasted overnight and were given po either vehicle (1% methocel or 5% Tween 80) or a test compound. One hr later, a line was drawn using a permanent marker at the level above the ankle in one hind paw to define the area of the paw to be monitored. The paw volume (V0) was measured using a plethysmometer (Ugo-Basile, Italy) based on the principle of water displacement. The animals were then injected

- 45 -

subplantarily with 50 µl of 1% carrageenan solution in saline (FMC Corp, Maine) into the paw using an insulin syringe with a 25-gauge needle (i.e. 500 µg carrageenan per paw). Three hr later, the paw volume (V3) was measured and the increases in paw volume (V3 - V0) were calculated. The animals were sacrificed by CO₂ asphyxiation and the absence or presence of stomach lesions scored. Data were compared with the vehicle-control values and percent inhibition calculated. ED₅₀ values were used for comparison. All treatment groups were coded to eliminate observer bias.

NSAID-Induced Gastrophathy in Rats

Rationale

The major side effect of conventional NSAIDs is their ability to produce gastric lesions in man. This action is believed to be caused by inhibition of COX-1 in the gastrointestinal tract. Rats are particularly sensitive to the actions of NSAIDs. In fact, rat models have been used commonly in the past to evaluate the gastrointestinal side effects of current conventional NSAIDs. In the present assay, NSAID-induced gastrophathy is observed by measuring fecal ⁵¹Cr excretion after systemic injection of ⁵¹Cr-labeled red blood cells. Fecal ⁵¹Cr excretion is a well-established and sensitive technique to detect gastrophathy in animals and man.

5	<p>Male Sprague Dawley rats (150 - 200 g) are administered orally a test compound either once (acute dosing) or b.i.d. for 5 days (chronic dosing). Immediately after the administration of the last dose, the rats are injected via a tail vein with 0.5 mL of ^{51}Cr-labeled red blood cells from a donor rat. The animals are placed individually in metabolism cages with food and water <i>ad lib</i>. Feces are collected for a 48 h period and ^{51}Cr fecal excretion is calculated as a percent of total injected dose.</p>
10	<p>^{51}Cr-labeled red blood cells are prepared using the following procedures. Ten mL of blood is collected in heparinized tubes via the vena cava from a donor rat. Plasma is removed by centrifugation and replenished with equal volume of HBSS. The red blood cells are incubated with 400 μCi of sodium ^{51}Cr chromate for 30 min at 37°C. At the end of the incubation, the red blood cells are washed twice with 20 mL HBSS to remove free sodium ^{51}Cr chromate. The red blood cells are finally reconstituted in 10 mL HBSS and 0.5 mL of the solution (about 20 μCi) is injected per rat.</p>
20	<p><u>Protein-Losing Gastropathy in Squirrel Monkeys</u></p>
	<p><u>Rationale</u></p>
25	<p>Protein-losing gastropathy (manifested as appearance of circulating cells and plasma proteins in the GI tract) is a significant and dose-limiting adverse response to standard NSAIDs. This can be quantitatively assessed by intravenous administration of $^{51}\text{CrCl}_3$ solution. This isotopic ion can avidly bind to cell and serum globins and cell endoplasmic reticulum. Measurement of radioactivity appearing in feces collected for 24 h after administration of the isotope thus provides a sensitive and quantitative index of protein-losing gastropathy.</p>
30	<p><u>Methods</u></p>
	<p>Groups of male squirrel monkeys (0.8 to 1.4 kg) are treated by gavage with either 1% methocel or 5% Tween 80 in H₂O</p>

no apparent inflammatory conditions and had not taken any NSAIDs for venipuncture from both male and female volunteers. The subjects had fresh blood was collected in heparinized tubes by

A. COX-2 (LPS-induced PGE2 production)

METHOD 30

following blood clotting (COX-1) in the same assay.

measuring the levels of PGE2 after LPS induction (COX-2) and TxB2 degree of selectivity by the test compound can be determined by examined and used as an index for COX-1 activity. Therefore, the test compounds on TxB2 levels following blood clotting can be of thromboxane B2 (TxB2) via activation of COX-1. Thus, the effect of thrombin-mediated mechanism. This reaction results in the production immediately following blood clotting, platelets are activated through a platelets in whole blood contain a large amount of the COX-1 enzyme. effect of selective COX-2 inhibitors on PGE2 production. As well, which induces COX-2. This assay can be used to evaluate the inhibitory after incubation of human whole blood with LPS (lipopolysaccharide), PGE2 production in normal blood. These inhibitors are active only consistent with the observation that COX-2 inhibitors have no effect on normal human blood does not contain the COX-2 enzyme. This is compounds such as selective COX-2 inhibitors. Studies have shown that appropriate for the study of biochemical efficacy of anti-inflammatory Human whole blood provides a protein and cell-rich milieu

Rationale 10

Human Whole Blood (HWP) Assay

and plasma concentrations of drug measured by RP-HPLC.

counting. Venous blood is sampled 1 h and 8 h after the last drug dose, 24 h in a metabolism cage and assessed for excreted ⁵¹Cr by gamma-administered 1 h after the last drug/vehicle dose, and feces collected for mg/kg b.i.d. for 5 days. Intravenous ⁵¹Cr (5 µCi/kg in 1 ml/kg PBS) is vehicles, (3 ml/kg b.i.d.) or test compounds at doses from 1 - 100

at least 7 days prior to blood collection. Plasma was immediately obtained from a 2mL blood aliquot to use as blank (basal levels of PGE₂). The remaining blood was incubated with LPS (100 µg/ml final concentration, Sigma Chem, #L-2630 from E. coli; diluted in 0.1% BSA-Phosphate buffered saline) for 5 minutes at room temperature. Five hundred µL aliquots of blood were incubated with either 2 µL vehicle (DMSO) or 2 µL of a test compound at final concentrations varying from 10nM to 30µM for 24 hours at 37°C. At the end of the incubation, the blood was centrifuged at 12,000 x g for 5 minutes to obtain plasma. A 100 µL aliquot of plasma was mixed with 400 µL of methanol for protein precipitation. The supernatant was obtained and was assayed for PGE₂ using a radioimmunoassay kit (Amersham, RPA#530) after conversion of PGE₂ to its methyl oximate derivative according to the manufacturer's procedure.

1 5 B. COX-1 (Clotting-induced TxB₂ production)

2 0 Fresh blood was collected into vacutainers containing no anticoagulants. Aliquots of 500 µL were immediately transferred to siliconized microcentrifuge tubes preloaded with 2 µL of either DMSO or a test compound at final concentrations varying from 10nM to 30 µM. The tubes were vortexed and incubated at 37°C for 1 hour to allow blood to clot. At the end of incubation, serum was obtained by centrifugation (12,000 x g for 5 min.). A 100 µL aliquot of serum was mixed with 400 µL of methanol for protein precipitation. The supernatant was obtained and was assayed for TxB₂ using a enzyme immunoassay kit (Cayman, #519031) according to the manufacturer's instruction.

3 0 Compounds of the present invention are inhibitors of COX-2 and are thereby useful in the treatment of COX-2 mediated diseases as enumerated above. The activities of the compounds against cyclooxygenase may be seen in the representative results shown below. In the assay, inhibition is determined by measuring the amount of prostaglandin E₂ (PGE₂) synthesized in the presence of A.A., COX-1

of COX-2 and a putative inhibitor. The IC₅₀ values represent the concentration of putative inhibitor required to return PGE₂ synthesis to 50% of that obtained as compared to the uninhibited control. The results for inhibition of PGE₂ production may be seen in Table II.

Table II

Example	HWB Cox-2 IC ₅₀ (μM)	HWB Cox-1 IC ₅₀ (μM)	Rat Paw Edema ED ₅₀ (mg/kg)
4	1.27	>90	1.5
5	1.41	>90	1.8
6	2.42		1.4
10	<0.37		1.9
15	<0.37	>30	2.8
16	0.47		
17	0.86		
18	0.77		
20	1.95		
25	2.17	>100	2.27
26	2.11		
27	5.91		
28	2.78		
29	3.41		
30	3.36		
31	6.86		
34	3.21		
35	17.05		
40	1.18		
41	3.48		
44	21.05		
45	<0.41		6.4
46	0.88	75.5	1.89
47	1.70	38.2	

- 50 -

48	4.37	>100	5.56
49	4.71		10
50	2.12		1.53
51	1.57	66	
52	17.8		
53	4.43		3.65
54	15.2		
55	8.75		
56	3.46		
57	2.75	>100	
58	2.28	>100	2.2
59	1.30		1.80
60	1.55		0.56
61			2.79
63	2.22		

The following abbreviations have the indicated meanings

5	Ac =	acetyl
	Bn =	benzyl
	DBU =	diazabicyclo[5.4.0]undec-7-ene
	Et ₃ N =	triethylamine
	HBSS =	Hank's balanced salt solution
	HWB =	human whole blood
10	KHMDS =	potassium hexamethyldisilazane
	LDA =	lithium diisopropylamide
	MMPP =	magnesium monoperoxyphthalate
	Ms =	methanesulfonyl = mesyl
	MsO =	methanesulfonate = mesylate
15	NSAID =	non-steroidal anti-inflammatory drug
	PCC =	pyridinium chlorochromate
	PDC =	pyridinium dichromate
	Ph =	phenyl
	r.t. =	room temperature

- 51 -

rac.	=	racemic
TFA	=	trifluoroacetic acid
TfO	=	trifluoromethanesulfonate = triflate
Th	=	2- or 3-thienyl
THF	=	tetrahydrofuran
TLC	=	thin layer chromatography
Ts	=	p-toluenesulfonyl = tosyl
TsO	=	p-toluenesulfonate = tosylate
Tz	=	1H (or 2H)-tetrazol-5-yl
C ₃ H ₅	=	allyl
-SO ₂ Me	=	methyl sulfone
-SO ₂ NH ₂	=	sulfonamide

Alkyl group abbreviations

1.5	Me	=	methyl
	Et	=	ethyl
	n-Pr	=	normal propyl
	i-Pr	=	isopropyl
	n-Bu	=	normal butyl
2.0	i-Bu	=	isobutyl
	s-Bu	=	secondary butyl
	t-Bu	=	tertiary butyl
	c-Pr	=	cyclopropyl
	c-Bu	=	cyclobutyl
2.5	c-Pen	=	cyclopentyl
	c-Hex	=	cyclohexyl

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) all operations were carried out at room or ambient temperature, that is, at a temperature in the range 18-25°C;

- (ii) evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 pascals: 4.5-30 mm Hg) with a bath temperature of up to 60°C; (iii) the course of reactions was followed by thin layer chromatography (TLC) and reaction times are given for illustration only; (iv) melting points are uncorrected and 'd' indicates decomposition; the melting points given are those obtained for the materials prepared as described; polymorphism may result in isolation of materials with different melting points in some preparations; (v) the structure and purity of all final products were assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR) spectrometry or microanalytical data; (vi) yields are given for illustration only; (vii) when given, NMR data is in the form of delta (δ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 300 MHz or 400 MHz using the indicated solvent; conventional abbreviations used for signal shape are: s. singlet; d. doublet; t. triplet; m. multiplet; br. broad; etc.: in addition "Ar" signifies an aromatic signal; (viii) chemical symbols have their usual meanings; the following abbreviations have also been used v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (liter(s)), mL (milliliters), g (gram(s)), mg (milligrams(s)), mol (moles), mmol (millimoles), eq (equivalent(s)).
- 30 With regard to the preparation of certain starting materials, reference can be made to WO 95/00501, published January 5, 1995 or to US 5,474,995 issued December 12, 1995 which are hereby incorporated by reference.

EXAMPLE 1

- Benzoic acid 3-(4-(methylsulfonyl)phenyl)-5-oxo-4-phenyl-2,5-dihydrofuran-2-yl ester
- Step 1:** 3-(Phenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone
 To a solution of phenylacetic acid (27.4 g, 201 mmol) and 2-bromo-1-(4-(methylsulfonyl)phenyl)ethanone (WO 9500501, Ex. 9 Step 1, hereby incorporated by reference) (60 g, 216 mmol, 1.075 eq.) in acetonitrile (630 mL) at 25 °C was added slowly Et₃N (30.8 mL, 1.1 eq.). The mixture was stirred for 20 min. at r.t. and then cooled in an ice bath. DBU (60.1 mL, 3 eq.) was slowly added. After stirring for 20 min. in the ice bath, the reaction was complete and the mixture was acidified with 1N HCl (color changes from dark brown to yellow). Then 2.4 L of ice and water were added, stirred for a few minutes, then the precipitate was filtered and rinsed with water (giving 64 g of crude wet product). The solid was dissolved in 750 mL of CH₂Cl₂ (dried over MgSO₄, filtered) and 300 g of silica gel was added. The solvent was evaporated to near dryness (silica gel a bit sticky) and the residue was applied on top of a silica gel plug (sintered glass funnel) and eluted with 10% EtOAc/CH₂Cl₂, giving after evaporation of the solvent and a swish in EtOAc, 36.6 g (58%) of the title compound.
- Analysis** calculated for C₁₇H₁₄O₄S
 C, 64.95; H, 4.49; S, 10.20
Found: C, 64.63; H, 4.65; S, 10.44
- Step 2:** Benzoic acid 3-(4-(methylsulfonyl)phenyl)-5-oxo-4-phenyl-2,5-dihydrofuran-2-yl ester
 A mixture of 0.16 g of the product from Step 1, 0.18 mL of DBU and 0.31 g of benzoylperoxide in 2 mL of CH₂Cl₂ was stirred for 3.5 h at r.t.. The reaction mixture was then diluted with 50 mL of EtOAc and washed with 50 mL of 20% NH₄OAc solution. The organic layer was dried over MgSO₄, filtered and concentrated. The residue

- 54 -

was purified by silica gel flash chromatography, eluting with 45% EtOAc/hexane to give 92 mg of the title compound as a white solid.

¹H NMR (d6-acetone, 400 MHz) δ 7.95 - 8.08 (5H, m), 7.85 (1H, s), 7.79 (2H, d), 7.60 - 7.72 (2H, m), 7.41 - 7.55 (6H, m), 3.14 (3H, s).

EXAMPLE 2

5-Hydroxy-4-(4-(methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone 10

To a solution of 80 mg of the product from Step 2 in example 1 in 4 mL THF and 2 mL MeOH was added 0.5 mL of 2N aqueous NaOH solution. After stirring for 1h at r.t., the reaction mixture was treated with 5 mL of 20% aqueous NH₄OAc solution and extracted with 20 mL of EtOAc. The EtOAc layer was dried over MgSO₄, filtered and concentrated. The residue was purified by silica gel flash chromatography, eluting with 55% EtOAc/hexane to provide 10 mg of the title compound as a white solid.

¹H NMR (d6-acetone, 400 MHz) δ 7.98 (2H, d), 7.75 (2H, d), 7.40 (5H, m), 7.00 (1H, s), 6.76 (1H, s), 3.18 (3H, s).

EXAMPLE 3

5-Hydroxy-3-(3,4-difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone 25

¹H NMR (d6-acetone, 400 MHz) δ 8.01 (2H, d), 7.76 (2H, d), 7.34 - 7.48 (2H, m), 7.20 - 7.28 (1H, m), 7.10 (1H, s), 6.76 (1H, s), 3.17 (3H, s).

EXAMPLE 4

- 55 -

5-Hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone

5 A mixture of 2-bromo-1-(4-methylsulfonylphenyl)-propan-1-one (prepared using the methodology of WO 9500501, Ex. 9 Step1) (8.7 g) and phenyl acetic acid (5 g) in 150 mL of CH₃CN was treated with 8.5 mL of Et₃N. The reaction mixture was stirred overnight at r.t. and then 12 mL of DBU was added dropwise over 2 min. After stirring for 1 h at r.t. O₂ was bubbled into the mixture until it became colorless (in 45 min.). The reaction mixture was then poured into a solution of 80 mL 1N HCl and 100 mL of brine, and extracted with 500 mL of 1:1 EtOAc/hexane. The extract was dried over MgSO₄, filtered and concentrated. The crude product was swished from 1:4 EtOAc/hexane (200 mL) to give 7.2 g of the title product as a white solid.

¹H NMR (d₆-acetone, 400 MHz) δ 7.98 (2H, d), 7.76 (2H, d), 7.32 (5H, m), 6.86 (1H, s), 3.18 (3H, s), 1.70 (3H, s).

EXAMPLE 5

3-(4-Fluorophenyl)-5-hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

¹H NMR (d₆-acetone, 300 MHz) δ 7.98 (2H, d), 7.78 (2H, d), 7.42 (2H, dd), 7.12 (2H, t), 6.86 (1H, s), 3.16 (3H, s), 1.66 (3H, s).

EXAMPLE 6

3-(4-Chlorophenyl)-5-hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

A mixture of 2-bromo-1-(4-methylsulfonylphenyl)-propan-1-one (prepared using the methodology of WO 9500501, Ex. 9 Step1) (53.8 g) and 4-chlorophenyl acetic acid (33.9 g) in 500 mL of CH₃CN was treated with 28 mL of Et₃N. The reaction mixture was stirred

- 56 -

overnight at r.t. then diluted with 800 mL of CH₃CN and cooled to 0 °C. 73 mL of DBU was added dropwise over 20 min. After stirring for 1 h at r.t. air was bubbled into the mixture and it was allowed to warm to r.t. After 4.5 h, the reaction mixture was then poured into a solution of 800 mL 1N HCl and extracted with 500 mL of EtOAc. The extract was washed with brine, dried over MgSO₄, filtered and concentrated. The crude product was swished from ether/hexane to give 56.3 g of the title product as a white solid.

¹H NMR (d6-acetone, 400 MHz) δ 8.00 (2H, d), 7.78 (2H, d), 7.38 (3H, s), 6.90 (1H, s), 3.16 (3H, s), 1.67 (3H, s).

EXAMPLE 7

3-(3,4-Difluorophenyl)-5-hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

¹H NMR (d6-acetone, 300 MHz) δ 8.02 (2H, d), 7.82 (2H, d), 7.25 - 7.42 (2H, m), 7.15 (1H, m), 6.92 (1H, s), 3.16 (3H, s), 1.68 (3H, s).

EXAMPLE 8

3-(3-Fluorophenyl)-5-hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

¹H NMR (d6-acetone, 300 MHz) δ 8.00 (2H, d), 7.80 (2H, d), 7.30 - 7.42 (1H, m), 7.10 - 7.22 (3H, m), 6.92 (1H, s), 3.16 (3H, s), 1.70 (3H, s).

EXAMPLE 9

3-(3,5-Difluorophenyl)-5-hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

¹H NMR (d6-acetone, 400 MHz) δ 8.04 (2H, d), 7.82 (2H, d), 6.95 - 7.10 (3H, m), 6.94 (1H, s), 3.18 (3H, s), 1.70 (3H, s).

EXAMPLE 10

5 5-Methoxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone

To a solution of 5-hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone (Example 4) (1.0 g) in 120 mL of MeOH was added 0.1 mL of concentrated H₂SO₄. The mixture was heated to reflux for 3 days and then treated with 2 mL of Et₃N. Methanol was removed under reduced pressure and the residue was purified by silica gel flash chromatography eluted with 4:1 toluene/EtOAc. After a swish from 2:1 hexane/EtOAc, 0.8 g of the title compound was obtained as a white solid.

¹H NMR (d₆-acetone, 300 MHz) δ 7.98 (2H, d), 7.70 (2H, d), 7.35 - 7.65 (5H, m), 3.45 (3H, s), 3.15 (3H, s), 1.66 (3H, s).

EXAMPLE 11

20 3-(4-Chlorophenyl)-5-methoxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

¹H NMR (d₆-acetone, 400 MHz) δ 7.98 (2H, d), 7.70 (2H, d), 7.36 - 7.46 (4H, m), 3.47 (3H, s), 3.16 (3H, s), 1.68 (3H, s).

EXAMPLE 12

30 3-(3,4-Difluorophenyl)-5-methoxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

¹H NMR (d₆-acetone, 300 MHz) δ 8.00 (2H, d), 7.74 (2H, d), 7.40 - 7.50 (1H, m), 7.28 - 7.40 (1H, m), 7.21 - 7.29 (1H, m), 3.47 (3H, s), 3.18 (3H, s), 1.65 (3H, s).

EXAMPLE 13

3-(3-Fluorophenyl)-5-methoxy-4-(4-(methanesulfonyl)phenyl)-2-(5H)-furanone

¹H NMR (d6-acetone, 300 MHz) δ 7.98 (2H, d), 7.71 (2H, d), 7.38-7.45 (1H, m), 7.25 - 7.29 (3H, m), 3.49 (3H, s), 3.16 (3H, s), 1.68 (3H, s).

Calc: C, 59.33; H, 4.70

Found: C, 60.12; H, 4.57

EXAMPLE 14

3-(3,5-Difluorophenyl)-5-methoxy-4-(4-(methanesulfonyl)phenyl)-2-(5H)-furanone

¹H NMR (d6-acetone, 300 MHz) δ 8.01 (2H, d), 7.23 (2H, d), 7.05 - 7.14 (3H, m), 3.48 (3H, s), 3.16 (3H, s), 1.66 (3H, s).

3-(4-Fluorophenyl)-5-methoxy-4-(4-(methanesulfonyl)phenyl)-2-(5H)-furanone

¹H NMR (d6-acetone, 300 MHz) δ 8.00 (2H, d), 7.72 (2H, d), 7.44 - 7.52 (2H, m), 7.12 - 7.20 (2H, m), 3.48 (3H, s), 3.17 (3H, s), 1.66 (3H, s).

Calc: C, 60.60; H, 4.55

Found: C, 60.55; H, 4.50

EXAMPLE 16

5-Ethoxy-3-(4-Fluorophenyl)-4-(4-(methanesulfonyl)phenyl)-2-(5H)-furanone

30

- 59 -

¹H NMR (d6-acetone, 300 MHz) δ 7.99 (2H, d), 7.72 (2H, d), 7.44 - 7.53 (2H, m), 7.12 - 7.20 (2H, m), 3.68 - 3.78 (2H, m), 3.16 (3H, s), 1.67 (3H, s), 1.28 (3H, t).
 Calc: C, 61.53; H, 4.91
 Found: C, 60.87; H, 4.90

EXAMPLE 17

3-(4-Fluorophenyl)-5-methyl-4-(4-(methylsulfonyl)phenyl)-5-propoxy-2-(5H)-furanone

¹H NMR (d6-acetone, 300 MHz) δ 7.96 (2H, d), 7.70 (2H, d), 7.42 - 7.51 (2H, m), 7.10 - 7.20 (2H, m), 3.62 (2H, t), 3.16 (3H, s), 1.62 - 1.76 (2H, m), 1.66 (3H, s), 1.00 (3H, t).
 Calc: C, 62.36; H, 5.23
 Found: C, 61.86; H, 5.20

EXAMPLE 18

3-(4-Fluorophenyl)-5-isopropoxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

¹H NMR (d6-acetone, 300 MHz) δ 7.98 (2H, d), 7.79 (2H, d), 7.40 - 7.51 (2H, m), 7.11 - 7.19 (2H, m), 4.12 - 4.23 (1H, m), 3.15 (3H, s), 1.70 (3H, s), 1.26 (3H, d), 1.21 (3H, d).
 Calc: C, 62.36; H, 5.23
 Found: C, 62.31; H, 5.33

EXAMPLE 19

5-Methyl-5-methylthio-4-(4-(methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone

¹H NMR (d6-acetone, 400 MHz) δ 8.00 (2H, d), 7.81 (2H, d), 7.26 - 7.40 (5H, m), 3.16 (3H, s), 2.14 (3H, s), 1.80 (3H, s).

- 60 -

EXAMPLE 20

5-Ethylthio-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone
¹H NMR (d6-acetone, 300 MHz) δ 8.00 (2H, d), 7.73 (2H, d), 7.28 - 7.42 (5H, m), 3.16 (3H, s), 2.56 - 2.35 (2H, m), 1.78 (3H, s), 1.28 (3H, t).

EXAMPLE 21

5-Ethyl-5-hydroxy-4-(4-(methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone
¹H NMR (d6-acetone, 300 MHz) δ 7.96 (2H, d), 7.80 (2H, d), 7.30-7.40 (5H, m), 6.85 (1H, s), 3.15 (3H, s), 2.0-2.15 (1H, m), 1.8-1.92 (1H, m), 0.89 (3H, t).

EXAMPLE 22

5-Ethyl-3-(3-fluorophenyl)-5-hydroxy-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone
¹H NMR (d6-acetone, 300 MHz) δ 8.00 (2H, d), 7.80 (2H, d), 7.34-7.44 (1H, m), 7.12-7.19 (3H, m), 6.88 (1H, s), 3.15 (3H, s), 2.0-2.15 (1H, m), 1.8-1.92 (1H, m), 0.89 (3H, t).

EXAMPLE 23

Acetic acid, 3-(4-(methylsulfonyl)phenyl)-2-methyl-5-oxo-4-phenyl-2,5-dihydrofuran-2-yl ester
¹H NMR (d6-acetone, 300 MHz) δ 8.00 (2H, d), 7.65 (2H, d), 7.40-7.52 (5H, m), 3.15 (3H, s), 2.15 (3H, s), 1.83 (3H, s).

- 61 -

EXAMPLE 24

5-Hydroxy-5-methyl-4-((4-methylsulfonyl)phenyl)-3-(2-naphthyl)-2-(5H)-furanone

¹H NMR (d₆-acetone, 300 MHz) δ 8.08 (1H, s), 7.97 (2H, m), 7.85 (6H, m), 7.52 (2H, m), 7.30 (1H, dd), 3.14 (3H, s), 1.72 (3H, s).

Calc for C₂₂H₁₈O₅•1/2 H₂O

C, 65.50; H, 4.75

Found: C, 65.24; H, 4.66

5

10

EXAMPLE 25

Sodium 2-(4-fluorophenyl)-3-((4-methylsulfonyl)phenyl)-4-oxo-2-pentenoate

15

To a solution of 3-(4-fluorophenyl)-5-hydroxy-5-methyl-4-((4-methylsulfonyl)phenyl)-2-(5H)-furanone (Example 5) (210 mg) in 4 mL of absolute ethanol was added 0.58 mL of a 1.00M sodium hydroxide solution. The resulting solution was concentrated to give a solid, which was subsequently dissolved in 4 mL of water. Lyophilization provided 210 mg of the title compound as a light orange solid.

¹H NMR (d₆-DMSO, 300 MHz) δ 7.68 (2H, m), 7.18 (2H, m), 7.03 (2H, m), 6.91 (2H, d), 3.13 (3H, s), 2.35 (3H, s).

EXAMPLE 26

Calc: C, 56.84; H, 3.71

Found: C, 56.58; H, 3.83

30

EXAMPLE 28

Calc: C, 50.34; H, 3.78

Found: C, 50.00; H, 3.75

35

- 62 -

EXAMPLE 29

Calc: C, 53.76; H, 3.72; N, 3.69
 Found: C, 52.91; H, 3.71; N, 3.53

EXAMPLE 30

Calc: C, 51.08; H, 3.57
 Found: C, 51.02; H, 3.74

EXAMPLE 31

Calc: C, 53.27; H, 3.53
 Found: C, 53.32; H, 3.67

EXAMPLE 32

Calc: C, 58.16; H, 4.37
 Found: C, 57.71; H, 4.31

EXAMPLE 33

Calc: C, 54.48; H, 3.56
 Found: C, 54.19; H, 3.60

EXAMPLE 34

Calc: C, 59.12; H, 4.38; N, 4.06
 Found: C, 58.40; H, 4.34; N, 3.96

EXAMPLE 35

Calc for C₁₉H₁₈O₆S•1/2 H₂O
 C, 59.52; H, 4.99
 Found: C, 59.65; H, 4.93

EXAMPLE 38

5 Calc: C, 64.85; H, 4.90
 Found: C, 64.22; H, 4.86

EXAMPLE 39

10

Calc for $C_{20}H_{16}O_{5.5} \cdot 1/2 H_2O$
 C, 58.66; H, 4.18
 Found: C, 58.89; H, 4.27

EXAMPLE 40

15

 Calc: C, 60.95; H, 4.85
 Found: C, 60.64; H, 4.79

EXAMPLE 41

20

 Calc: C, 59.98; H, 4.03
 Found: C, 58.96; H, 3.78

EXAMPLE 44

25

 Calc: C, 54.84; H, 4.03
 Found: C, 54.34; H, 4.28

EXAMPLE 45

35 Calc: C, 54.05; H, 3.63

- 64 -

EXAMPLE 46

Found: C, 54.18; H, 3.66

5

m.p. 175-176°C

EXAMPLE 47

10

Calc: C, 58.44; H, 4.65

Found: C, 58.41; H, 4.72

15

EXAMPLE 48

Calc: C, 58.44; H, 4.65

Found: C, 58.41; H, 4.72

20

EXAMPLE 49

m.p. 124-125°C

25

EXAMPLE 50

m.p. 153-154°C

30

EXAMPLE 51

m.p. 123-124°C

35

EXAMPLE 52

- 65 -

m.p. 131-132°C

EXAMPLE 53

5

m.p. 168-169°C

EXAMPLE 54

10

m.p. 197-198°C

EXAMPLE 55

15

Calc: C, 57.86; H, 4.09; N, 8.13
Found: C, 58.00; H, 4.21; N, 8.41

EXAMPLE 56

20

Calc: C, 53.41; H, 3.77; N, 7.50
Found: C, 53.65; H, 4.15; N, 7.51

EXAMPLE 57

25

m.p. 130-131°C

EXAMPLE 58

30

¹H NMR (d₆-DMSO, 300 MHz) δ 7.64 (m, 2H), 7.17 (m, 2H), 7.05 (m, 5H), 3.12 (s, 3H), 2.35 (s, 3H).

35

- 66 -

EXAMPLE 59

Sodium 2-(4-chlorophenyl)-3-(((4-methylsulfonyl)phenyl)-4-oxo-2-pentenoate

5

To a solution of 3-(4-chlorophenyl)-5-hydroxy-5-methyl-4-(4-methylsulfonyl)phenyl-2-(5H)-furanone (Example 6) (50.3 g) in 200 mL of ethanol and 200 mL water was added 13.2 mL of a 10.0 M sodium hydroxide solution while cooling in an ice-bath. The resulting solution was concentrated to give a solid, which was subsequently dissolved in 200 mL of water. Lyophilization provided 52.5 g of the title compound as an off-white solid.

10

¹H NMR (d₆-DMSO, 300 MHz) δ 7.70 (2H, m), 7.21 (2H, m), 7.17 (2H, m), 7.03 (2H, d), 3.14 (3H, s), 2.34 (3H, s).

15

EXAMPLE 60

¹H NMR (d₆-DMSO, 400 MHz) δ 7.72 (m, 2H), 7.30 (m, 2H), 7.25 (m, 2H), 6.87 (m, 1H), 3.16 (s, 3H), 2.31 (s, 3H).

20

EXAMPLE 61

¹H NMR (d₆-DMSO, 400 MHz) δ 7.71 (m, 2H), 7.69 (m, 2H), 7.24 (m, 2H), 6.96 (m, 2H), 3.30 (s, 3H), 2.29 (s, 3H).

25

EXAMPLE 63

¹H NMR (d₆-acetone, 400 MHz) δ 7.70 (m, 2H), 7.23 (m, 3H), 7.10 (m, 1H), 6.86 (m, 1H), 3.13 (s, 3H), 2.32 (s, 3H).

35

EXAMPLE 64

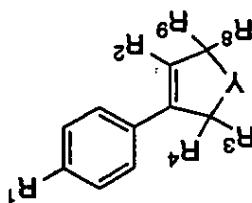
- 67 -

¹H NMR (d₆-acetone, 400 MHz) δ 7.65 (m, 2H), 7.16 (m, 2H), 6.93 (m, 2H), 6.13 (m, 2H), 3.15 (s, 3H), 2.38 (s, 3H).

5

WHAT IS CLAIMED IS:

1. A compound of formula I



5

or a pharmaceutically acceptable salt thereof

wherein:

Y is selected from the group consisting of

10

(a) C(R1)(R12),

(b) oxygen,

(c) sulfur,

R1 is selected from the group consisting of

15

(a) S(O)2CH3,

(b) S(O)2NH2,

(c) S(O)2NHC(O)CF3,

(d) S(O)(NH)NH2,

(e) S(O)(NH)NHC(O)CF3,

(f) S(O)2NHMe

(g) P(O)(CH3)NH2,

(h) P(O)(CH3)2,

(i) C(S)NH2;

25

R2 is selected from the group consisting of

(a) C1-10alkyl,

(b) C3-10cycloalkyl,

(c) C2-10alkenyl,

(d) C2-10alkynyl,

(e) C3-10cycloalkenyl,

- 69 -

(f)	mono-, di-, tri- or tetra-substituted C ₃ -C ₁₀ cycloalkenyl wherein the substituent is selected from the group consisting of				
	(1) halo,	5			
	(2) C ₁ -6alkoxy,				
	(3) C ₁ -6alkylthio,				
	(4) CN,				
	(5) CF ₃ ,				
	(6) C ₁ -10alkyl,				
	(7) N ₃ ,	10			
	(8) -CO ₂ H,				
	(9) -CO ₂ -C ₁ -10alkyl,				
	(10) -C(R ₅)(R ₆)-OH,				
	(11) -C(R ₅)(R ₆)-O-C ₁ -4alkyl, and				
	(12) -C ₁ -10alkyl-CO ₂ -R ₅ ;	15			
	(13) benzyloxy,				
	(14) -O-(C ₁ -10alkyl)-CO ₂ R ₅ ,				
	(15) -O-(C ₁ -10alkyl)-NR ₅ R ₆ ,				
(g)	unsubstituted or mono-, di- or tri-substituted phenyl or naphthyl wherein the substituent is selected from the group consisting of	20			
	(1) halo,				
	(2) C ₁ -10alkoxy,				
	(3) C ₁ -10fluoroalkoxy,				
	(4) C ₁ -10alkylthio,	25			
	(5) CN,				
	(6) CF ₃ ,				
	(7) C ₁ -10alkyl,				
	(8) N ₃ ,				
	(9) -CO ₂ H,				
	(10) -CO ₂ -C ₁ -10alkyl,				
	(11) -C(R ₅)(R ₆)-OH,				
	(12) -C(R ₅)(R ₆)-O-C ₁ -4alkyl, and				
	(13) -C ₁ -6alkyl-CO ₂ -R ₅ ;	30			
	(14) -C(R ₅)(R ₆)-O-C ₁ -4alkyl, and				
	(15) -C ₁ -6alkyl-CO ₂ -R ₅ ;				

- 70 -

(h)	5	<p>unsubstituted or mono-, di- or tri-substituted heteroaryl wherein the heteroaryl is a monocyclic aromatic ring of 5 atoms, said ring having one hetero atom which is S, O, or N, and optionally 1, 2, or 3 additional N atoms; or the heteroaryl is a monocyclic ring of 6 atoms, said ring having one hetero atom which is N, and optionally 1, 2 or 3 additional N atoms, said substituents are selected from the group consisting of</p> <p>(1) halo, (2) C1-10alkyl, (3) C1-10alkoxy, (4) C1-10alkylthio, (5) CN, (6) CF₃, (7) N₃, (8) -C(R⁵)(R⁶)-OH, and (9) -C(R⁵)(R⁶)-O-C1-10alkyl;</p>
(i)	20	<p>an unsubstituted or a mono- or di- substituted benzoheterocycle in which the heterocycle is a 5, 6, or 7-membered ring which may contain 1 or 2 heteroatoms chosen independently from O, S, or N and which may contain a carbonyl group or a sulfonyl group; the said substituents are selected from the group consisting of</p> <p>(1) halo, (2) C1-10alkyl, (3) C1-10alkoxy, (4) C1-10alkylthio, (5) CN, (6) CF₃, (7) N₃, (8) -C(R⁵)(R⁶)-OH, and</p>
	30	

- 71 -

- (j) a heterocycloalkyl group of 5, 6 or 7 members which contains 1 or 2 heteroatoms chosen from O, S, or N and optionally contains a carbonyl group or a sulfonyl group. (k) an unsubstituted or a mono- or di- substituted benzocyclobutene in which the carbocycle is a 5, 6, or 7-membered ring which optionally contains a carbonyl group, the said substituents are selected from the group consisting of
- | | | | | | | | | | |
|-----|-----------|-----------------|------------------|---------------------|---------|-----------------------|----------------------|--|--|
| 1 0 | (1) halo, | (2) C1-10alkyl, | (3) C1-10alkoxy, | (4) C1-10alkylthio, | (5) CN, | (6) CF ₃ , | (7) N ₃ , | (8) -C(R ⁵)(R ⁶)-OH, and | (9) -C(R ⁵)(R ⁶)-O-C1-10alkyl; |
| 1 5 | | | | | | | | | |
| 2 0 | | | | | | | | | |
| | | | | | | | | | |
| 2 5 | | | | | | | | | |
| 3 0 | | | | | | | | | |
- R³ is hydrogen, C1-10alkyl, CH₂OR⁷, CN, CH₂CN, or C1-6fluoroalkyl, F, CONR⁷, unsubstituted or mono- or di-substituted phenyl, unsubstituted or mono or di-substituted benzyl, unsubstituted or mono- or di-substituted heteroaryl, unsubstituted or mono or di-substituted heteroarylthio, wherein the substituents are selected from the group consisting of
- R⁴ is

- 72 -

- (a) C1-10alkoxy,
 (b) C1-10fluoroalkoxy,
 (c) C1-10alkylthio,
 (d) -OH,
 (e) -OCOR⁷,
 (f) -SH,
 (g) -SCOR⁷,
 (h) -OCO₂R⁸,
 (i) -SCO₂R⁸,
 (j) OCONR⁷₂,
 (k) SCONR⁷₂,
 (l) C3-10cycloalkoxy, and
 (m) C3-10cycloalkylthio;
- 1 5 each R⁵ or R⁶ is independently selected from the group consisting of
 (a) hydrogen, and
 (b) C1-10alkyl,
 or R⁵ and R⁶ together with the carbon to which they are attached
 form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7
 atoms;
- 2 0 each R⁷ is independently selected from the group consisting of
 (a) hydrogen and
 (b) R⁸;
- 2 5 each R⁸ is independently selected from the group consisting of
 (a) C1-10alkyl,
 (b) phenyl or monosubstituted phenyl wherein the substituents
 may be halo, C1-10alkyl, C1-10alkoxy, C1-10alkylthio,
 CN, or CF₃,
 (c) benzyl or monosubstituted benzyl wherein the substituents
 may be halo, C1-10alkyl, C1-10alkoxy, C1-10alkylthio,
 CN, or CF₃, and
 (d) C3-10cycloalkyl
- 3 0 R⁹ and R¹⁰ are independently selected from the group consisting of:
 (a) hydrogen,

- 73 -

- (b) C1-10alkyl,
(c) C3-10cycloalkyl, or
R⁹ and R¹⁰ together form a double bonded O or S;
R¹¹ and R¹² are independently selected from the group consisting of:
(a) hydrogen,
(b) unsubstituted or mono- or di-substituted phenyl or
unsubstituted or mono- or di-substituted benzyl or
unsubstituted or mono- or di-substituted heteroaryl, said substituents
are selected from the group consisting of:
10 (1) halo,
(2) C1-10alkyl,
(3) C1-10alkoxy,
(4) C1-10alkylthio,
(5) CN,
(6) CF₃,
(7) N₃,
(8) -C(R¹³)(R¹⁴)-OH, and
(9) -C(R¹³)(R¹⁴)-O-C1-10alkyl, or
(c) C1-10alkyl, CH₂OR⁷, CN, CH₂CN, C1-10fluoroalkyl, F or
CONR^{7,2}, or
R¹¹ and R¹² together with the carbon to which they are attached
form a carbonyl or a saturated monocyclic carbon ring of
3, 4, 5, 6 or 7 atoms;
R¹³ and R¹⁴ are independently selected from the group consisting of:
(a) hydrogen,
(b) C1-10alkyl, or
R¹³ and R¹⁴ together with the carbon to which they are attached
form a carbonyl, -C(=S)-, or a saturated monocyclic carbon
ring of 3, 4, 5, 6, or 7 atoms.
30
2. A compound according to Claim 1
wherein:
35 Y is selected from the group consisting of

- 74 -

5	<p>R¹ is selected from the group consisting of</p> <p>(a) S(O)₂CH₃, (b) S(O)₂NH₂, (c) S(O)₂NHC(O)CF₃, (d) S(O)(NH)NH₂, (e) S(O)(NH)NHC(O)CF₃,</p>	10	<p>R² is selected from the group consisting of</p> <p>(a) C₃-10cycloalkyl, (b) C₃-8cycloalkenyl, (c) mono-, di- or tri-substituted C₃-C₈cycloalkenyl wherein the substituent is selected from the group consisting of</p>	15	<p>(1) halo, (2) C₁-galkoxy, (3) C₁-galkylthio, (4) CN, (5) CF₃, (6) C₁-galkyl, (7) N₃, (8) -CO₂H, (9) -CO₂-C₁-10alkyl, (10) -C(R⁵)(R⁶)-OH, (11) -C(R⁵)(R⁶)-O-C₁-4alkyl, and (12) -C₁-6alkyl-CO₂-R⁵;</p>	20	<p>(d) unsubstituted or mono-, di- or tri-substituted phenyl or naphthyl wherein the substituent is selected from the group consisting of</p> <p>(1) halo, (2) C₁-galkoxy, (3) C₁-galkylthio, (4) CN, (5) CF₃, (6) C₁-galkyl, (7) N₃, (8) -CO₂H, (9) -CO₂-C₁-10alkyl, (10) -C(R⁵)(R⁶)-OH, (11) -C(R⁵)(R⁶)-O-C₁-4alkyl, and (12) -C₁-6alkyl-CO₂-R⁵; (13) -O-(C₁-6alkyl)-CO₂R⁵,</p>	30	
---	--	----	--	----	---	----	--	----	--

30	(f) an unsubstituted or a mono- or di- substituted benzoheterocycle in which the heterocycle is a 5, 6, or 7-membered ring which may contain 1 or 2 heteroatoms chosen independently from O, S, or N and which may contain a carbonyl group or a sulfonyl group; the said substituents are selected from the group consisting of	(1) halo,
25	(1) halo, (2) C1-alkyl, (3) C1-alkoxy, (4) C1-alkylthio, (5) CN, (6) CF ₃ , (7) N ₃ , (8) -C(R ₅)(R ₆)-OH, and (9) -C(R ₅)(R ₆)-O-C1-6alkyl;	
20	(e) unsubstituted or mono-, di- or tri-substituted heteroaryl wherein the heteroaryl is a monocyclic aromatic ring of 5 atoms, said ring having one hetero atom which is S, O, or N, and optionally 1, 2, or 3 additional N atoms; or the heteroaryl is a monocyclic ring of 6 atoms, said ring having one hetero atom which is N, and optionally 1, 2 or 3 additional N atoms, said substituents are selected from the group consisting of	
15		
10	(4) CN, (5) CF ₃ , (6) C1-alkyl, (7) N ₃ , (8) -CO ₂ H, (9) -CO ₂ -C1-6alkyl, (10) -C(R ₅)(R ₆)-OH, (11) -C(R ₅)(R ₆)-O-C1-4alkyl, and (12) -C1-6alkyl-CO ₂ -R ₅ ; (13) -O-(C1-6alkyl)-CO ₂ R ₅ ,	
5		

- (2) C1-6alkyl,
(3) C1-6alkoxy,
(4) C1-6alkylthio,
(5) CN,
(6) CF₃,
(7) N₃,
(8) -C(R⁵)(R⁶)-OH, and
(9) -C(R⁵)(R⁶)-O-C1-6alkyl;
- (g) a heterocycloalkyl group of 5, 6 or 7 members which contains 1 or 2 heteroatoms chosen from O, S, or N and optionally contains a carbonyl group or a sulfonyl group. (h) an unsubstituted or a mono- or di- substituted benzocyclobutene in which the carbocycle is a 5, 6, or 7-membered ring which optionally contains a carbonyl group, the said substituents are selected from the group consisting of
- (1) halo,
(2) C1-6alkyl,
(3) C1-6alkoxy,
(4) C1-6alkylthio,
(5) CN,
(6) CF₃,
(7) N₃,
(8) -C(R⁵)(R⁶)-OH, and
(9) -C(R⁵)(R⁶)-O-C1-6alkyl;
- R³ is hydrogen, C1-6alkyl, CH₂OR⁷, CN, CH₂CN, or C1-6fluoroalkyl, F, CONR⁷, unsubstituted or mono- or di-substituted phenyl, unsubstituted or mono or di-substituted benzyl, unsubstituted or mono- or di-substituted heteroaryl, unsubstituted or mono or di-substituted heteroaryl, wherein the substituents are selected from the group consisting of
- (1) halo,
(2) C1-6alkyl,
(3) C1-6alkoxy,

- 77 -

5	R ⁴ is	(4) C1-6alkylthio, (5) CN, (6) CF ₃ , (7) N ₃ , (8) -C(R ⁵)(R ⁶)-OH, and (9) -C(R ⁵)(R ⁶)-O-C1-6alkyl;
10		(a) C1-6alkoxy, (b) C1-6alkylthio,
15		(c) -OH, (d) -OCOR ⁷ , (e) -SH, (f) -SCOR ⁷ , (g) -OCO ₂ R ⁸ , (h) -SCO ₂ R ⁸ , (i) OCONR ⁷ ₂ , and (j) SCONR ⁷ ₂ ;
20	each R ⁵ or R ⁶ is independently selected from the group consisting of	(a) hydrogen, and (b) C1-6alkyl,
25	or R ⁵ and R ⁶ together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;	
30	each R ⁷ is independently selected from the group consisting of	(a) hydrogen and (b) R ⁸ ;
	each R ⁸ is independently selected from the group consisting of	(a) C1-6alkyl, (b) phenyl or monosubstituted phenyl wherein the substituents may be halo, C1-6alkyl, C1-6alkoxy, C1-6alkylthio, CN, or CF ₃ ,

- (c) benzyl or monosubstituted benzyl wherein the substituents may be halo, C1-6alkyl, C1-6alkoxy, C1-6alkylthio, CN, or CF₃, and
- (d) C3-6cycloalkyl
- 5 R⁹ and R¹⁰ are independently selected from the group consisting of:

- (a) hydrogen,
 (b) C1-6alkyl,
 (c) C3-6cycloalkyl, or
- R⁹ and R¹⁰ together form a double bonded O;

- 10 R¹¹ and R¹² are independently selected from the group consisting of:

- (a) hydrogen,
 (b) C1-10alkyl, CH₂OR⁷, CN, CH₂CN, C1-6fluoroalkyl, F or CONR⁷₂; or

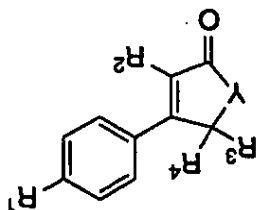
- 15 R¹¹ and R¹² together with the carbon to which they are attached form a carbonyl or a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;

- R¹³ and R¹⁴ are independently selected from the group consisting of:

- (a) hydrogen,
 (b) C1-6alkyl, or

- 20 R¹³ and R¹⁴ together with the carbon to which they are attached form a carbonyl or a saturated monocyclic carbon ring of 3, 4, 5, 6, or 7 atoms.

3. A compound according to Claim 2 of formula Ia



Ia

or a pharmaceutically acceptable salt thereof

- 79 -

wherein:	
Y is selected from the group consisting of	(a) C(R ¹¹)(R ¹²),
	(b) oxygen,
	(c) sulfur,
R ¹ is selected from the group consisting of	(a) S(O) ₂ CH ₃ ,
	(b) S(O) ₂ NH ₂ ,
	(c) S(O) ₂ NHC(O)CF ₃ ,
	(d) S(O)(NH)NH ₂ ,
	(e) S(O)(NH)NHC(O)CF ₃ ,
R ² is selected from the group consisting of	(a) C ₃ -cycloalkyl,
	(b) mono- or di- substituted C ₃ -C ₆ cycloalkenyl wherein the
substituent is selected from the group consisting of	(1) halo,
	(2) C ₁ -alkoxy,
	(3) C ₁ -alkylthio,
	(4) CN,
	(5) CF ₃ ,
	(6) C ₁ -6alkyl,
	(7) N ₃ ,
	(8) -CO ₂ H,
	(9) -CO ₂ -C ₁ -6alkyl,
	(10) -C(R ⁵)(R ⁶)-OH,
	(11) -C(R ⁵)(R ⁶)-O-C ₁ -4alkyl,
(c) unsubstituted or mono-, di- or tri-substituted phenyl or	
naphthyl wherein the substituent is selected from the group	
consisting of	(1) halo,
	(2) C ₁ -alkoxy,
	(3) C ₁ -4alkylthio,
	(4) CN,
	(5) CF ₃ ,
	(6) C ₁ -6alkyl,
	(7) N ₃ ,
	(8) -CO ₂ H,
	(9) -CO ₂ -C ₁ -6alkyl,
	(10) -C(R ⁵)(R ⁶)-OH,
	(11) -C(R ⁵)(R ⁶)-O-C ₁ -4alkyl,
3 0	
2 5	
2 0	
1 5	
1 0	
5	

- 80 -

- (5) CF₃,
 (6) C₁₋₆alkyl,
 (7) N₃,
 (8) -CO₂H,
 (9) -CO₂-C₁₋₄alkyl,
 (10) -C(R⁵)(R⁶)-OH,
 (11) -C(R⁵)(R⁶)-O-C₁₋₄alkyl, and
 (12) -C₁₋₄alkyl-CO₂-R⁵;
 (13) -O-(C₁₋₄alkyl)-CO₂R⁵,
- (d) 10 unsubstituted or mono-, di- or tri-substituted heteroaryl wherein the heteroaryl is a monocyclic aromatic ring of 5 atoms, said ring having one hetero atom which is S, O, or N, and optionally 1, 2, or 3 additional N atoms; or the heteroaryl is a monocyclic ring of 6 atoms, said ring having one hetero atom which is N, and optionally 1, 2 or 3 additional N atoms, said substituents are selected from the group consisting of
- (1) halo,
 (2) C₁₋₄alkyl,
 (3) C₁₋₄alkoxy,
 (4) C₁₋₄alkylthio,
 (5) CN,
 (6) CF₃,
 (7) N₃,
 (8) -C(R⁵)(R⁶)-OH, and
 (9) -C(R⁵)(R⁶)-O-C₁₋₄alkyl;
- (e) 20 an unsubstituted or a mono- or di- substituted benzoheterocycle in which the heterocycle is a 5, 6, or 7-membered ring which may contain 1 or 2 heteroatoms chosen independently from O, S, or N and which may contain a carbonyl group or a sulfonyl group; the said substituents are selected from the group consisting of
- (1) halo,
 (2) C₁₋₄alkyl,
- 30

5	(f)	a heterocycloalkyl group of 5, 6 or 7 members which contains 1 or 2 heteroatoms chosen from O, S, or N and optionally contains a carbonyl group or a sulfonyl group.
10	(g)	an unsubstituted or a mono- or di- substituted benzocarboxy in which the carbocycle is a 5, 6, or 7-membered ring which optionally contains a carbonyl group, the said substituents are selected from the group consisting of
15		(1) halo, (2) C ₁ -alkyl, (3) C ₁ -alkoxy, (4) C ₁ -alkylthio, (5) CN, (6) CF ₃ , (7) N ₃ , (8) -C(R ₅)(R ₆)-OH, and (9) -C(R ₅)(R ₆)-O-C ₁ -alkyl;
20		(1) halo, (2) C ₁ -alkyl, (3) C ₁ -alkoxy, (4) C ₁ -alkylthio, (5) CN, (6) CF ₃ , (7) N ₃ , (8) -C(R ₅)(R ₆)-OH, and (9) -C(R ₅)(R ₆)-O-C ₁ -alkyl;
25		R ³ is hydrogen, C ₁ -alkyl, CH ₂ OR ⁷ , CN, CH ₂ CN, or C ₁ -fluoroalkyl, F, CONR ⁷ ₂ , unsubstituted or mono- or di-substituted phenyl, unsubstituted or mono or di-substituted benzyl, unsubstituted or mono- or di-substituted heteroaryl, unsubstituted or di-substituted heteroaryl, wherein the substituents are selected from the group consisting of
30		(1) halo, (2) C ₁ -alkyl, (3) C ₁ -alkoxy, (4) C ₁ -alkylthio,

5	R ⁴ is	(5) CN, (6) CF ₃ , (7) N ₃ , (8) -C(R ⁵)(R ⁶)-OH, and (9) -C(R ⁵)(R ⁶)-O-C1-4alkyl;
10		(a) C1-4alkoxy, (b) C1-4alkylthio, (c) -OH, (d) -OCOR ⁷ , (e) -SH, (f) -SCOR ⁷ , (g) -OCO ₂ R ⁸ , (h) -SCO ₂ R ⁸ , (i) OCONR ⁷ ₂ , and (j) SCONR ⁷ ₂ ;
15		
20	each R ⁵ or R ⁶ is independently selected from the group consisting of	(a) hydrogen, and (b) C1-4alkyl,
25	each R ⁸ is independently selected from the group consisting of	(a) C1-6alkyl, (b) phenyl or monosubstituted phenyl wherein the substituents may be halo, C1-4alkoxy, C1-4alkylthio, CN, or CF ₃ , (c) benzyl or monosubstituted benzyl wherein the substituents may be halo, C1-4alkoxy, C1-4alkyl, C1-4alkylthio, CN, or CF ₃ ;
30	R ¹¹ and R ¹² are independently selected from the group consisting of:	(a) hydrogen, (b) C1-4alkyl, CH ₂ OR ⁷ , CN, CH ₂ CN, C1-4fluoroalkyl, F or CONR ⁷ ₂ ;

- 83 -

R¹³ and R¹⁴ are independently selected from the group consisting of:

- (a) hydrogen,
(b) C₁₋₄alkyl.

5 4. A compound according to Claim 3

wherein:

Y is selected from the group consisting of

- (a) C(R¹¹)(R¹²),

- (b) oxygen,

- (c) sulfur,

R¹ is selected from the group consisting of

- (a) S(O)CH₃,

- (b) S(O)NH₂,

- (c) S(O)NHCH(O)CF₃,

- (d) S(O)(NH)NH₂,

- (e) S(O)(NH)NHCH(O)CF₃,

R² is selected from the group consisting of

- (a) C₃₋₆cycloalkyl,

- (b) unsubstituted or mono-, di- or tri-substituted phenyl or

naphthyl wherein the substituent is selected from the group

consisting of

- (1) halo,

- (2) C₁₋₆alkoxy,

- (3) C₁₋₆alkylthio,

- (4) CN,

- (5) CF₃,

- (6) C₁₋₆alkyl,

- (7) N₃,

- (8) -CO₂H,

- (9) -CO₂-C₁₋₆alkyl,

- (10) -C(R⁵)(R⁶)-OH,

- (11) -C(R⁵)(R⁶)-O-C₁₋₄alkyl, and

- (12) -C₁₋₆alkyl-CO₂-R⁵;

- (13) -O-(C₁₋₆alkyl)-CO₂R⁵,

35

30

25

20

15

10

5

R³ is hydrogen, C₁-alkyl, CH₂OR⁷, CN, CH₂CN, or C₁-fluoroalkyl, F, CONR⁷₂, unsubstituted or mono- or di-substituted phenyl, unsubstituted or mono or di-substituted benzyl, wherein the substituents are selected from the group consisting of

- | | |
|---|---|
| 5 | (1) halo, |
| | (2) C ₁ -alkyl, |
| | (3) C ₁ -alkoxy, |
| | (4) C ₁ -alkylthio, |
| | (5) CN, |
| | (6) CF ₃ , |
| | (7) N ₃ , |
| | (8) -C(R ⁵)(R ⁶)-OH, and |
| | (9) -C(R ⁵)(R ⁶)-O-C ₁ -10alkyl; |

R⁴ is

- | | |
|-----|--|
| 1 5 | (a) C ₁ -alkoxy, |
| | (b) C ₁ -alkylthio, |
| | (c) -OH, |
| | (d) -OCOR ⁷ , |
| | (e) -SH, |
| | (f) -SCOR ⁷ , |
| | (g) -OCO ₂ R ⁸ , |
| | (h) -SCO ₂ R ⁸ , |
| | (i) OCONR ⁷ ₂ , and |
| | (j) SCONR ⁷ ₂ ; |
| 2 5 | each R ⁵ or R ⁶ is independently selected from the group consisting of |
| | (a) hydrogen, and |
| | (b) C ₁ -alkyl, |
| | each R ⁷ is independently selected from the group consisting of |
| | (a) hydrogen and |
| | (b) R ⁸ ; |
| 3 0 | each R ⁸ is independently selected from the group consisting of |
| | (a) C ₁ -alkyl, |

5	phenyl or monosubstituted phenyl wherein the substituents may be halo, C1-alkyl, C1-alkoxy, C1-alkylthio, CN, or CF ₃ , (c) benzyl or monosubstituted benzyl wherein the substituents may be halo, C1-alkyl, C1-alkoxy, C1-alkylthio, CN, or CF ₃ ,	5
10	R ¹¹ and R ¹² are independently selected from the group consisting of: (a) hydrogen, (b) C1-alkyl, CH ₂ OR ⁷ , CN, CH ₂ CN, C1-fluoroalkyl, F or CONR ⁷ ₂ ; or R ¹¹ and R ¹² together with the carbon to which they are attached form a carbonyl or a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms; R ¹³ and R ¹⁴ are independently selected from the group consisting of: (a) hydrogen, (b) C1-alkyl, or R ¹³ and R ¹⁴ together with the carbon to which they are attached form a carbonyl.	10
15		15
20	5. A compound according to Claim 4 wherein: Y is selected from the group consisting of (a) C(R ¹¹)(R ¹²), (b) oxygen, (c) sulfur, R ¹ is selected from the group consisting of (a) S(O)ZCH ₃ , (b) S(O)ZNH ₂ , (c) S(O)ZNHCH(O)CF ₃ , (d) S(O)(NH)NH ₂ , (e) S(O)(NH)NHCH(O)CF ₃ ; R ² is selected from the group consisting of	20
25		25
30		30

- 86 -

unsubstituted or mono-, di- or tri-substituted phenyl
wherein the substituent is selected from the group
consisting of

5	(1) halo, (2) C1-6alkoxy, (3) C1-6alkylthio, (4) CN, (5) CF ₃ , (6) C1-6alkyl, (7) N ₃ , (8) -CO ₂ H, (9) -CO ₂ -C1-6alkyl, (10) -C(R ⁵)(R ⁶)-OH, (11) -C(R ⁵)(R ⁶)-O-C1-4alkyl;	
10		
15	R ³ is hydrogen, C1-4alkyl, CH ₂ OR ⁷ , CN, CH ₂ CN, or C1-4fluoroalkyl, F, CONR ⁷ ₂ , unsubstituted or mono- or di-substituted phenyl, wherein the substituents are selected from the group consisting of	
20	(1) halo, (2) C1-4alkyl, (3) C1-4alkoxy, (4) C1-4alkylthio, (5) CF ₃ , (6) N ₃ , (7) -C(R ⁵)(R ⁶)-OH, and	
25	R ⁴ is	
30	(a) C1-4alkoxy, (b) C1-4alkylthio, (c) -OH, (d) -OCOR ⁷ , (e) -SH, (f) -SCOR ⁷ , (g) -OCO ₂ R ⁸ , (h) -SCO ₂ R ⁸ , (i) OCONR ⁷ ₂ , and	
35		

(j) CONR^7_2 :

each R^5 or R^6 is independently selected from the group consisting of

(a) hydrogen, and

(b) C1-alkyl,

5 each R^7 is independently selected from the group consisting of

(a) hydrogen and

(b) R^8 ;

each R^8 is independently selected from the group consisting of

(a) C1-alkyl,

10 (b) phenyl or monosubstituted phenyl wherein the substituents may be halo, C1-alkyl, C1-alkoxy, C1-alkylthio, CN, or

CF_3 ,

R^{11} and R^{12} are independently selected from the group consisting of:

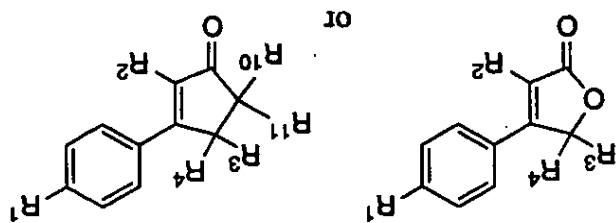
(a) hydrogen,

15 (b) C1-alkyl, CH_2OR^7 , CN, CH_2CN , C1-4fluoroalkyl, F or CONR^7_2 .

6. A compound according to Claim 5 of formula Ib or

Ic

20

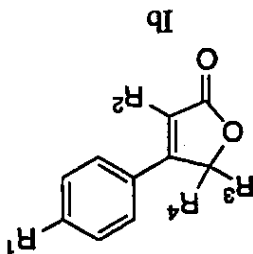


or a pharmaceutically acceptable salt thereof.

7. A compound according to Claim 6 of formula Ib

25

- 88 -



wherein:
R¹ is selected from the group consisting of

- (a) S(O)₂CH₃,
(b) S(O)₂NH₂,
(c) S(O)₂NHC(O)CF₃,
(d) S(O)(NH)NH₂;

R² is selected from the group consisting of

unsubstituted or mono-, di- or tri-substituted phenyl
wherein the substituent is selected from the group

consisting of

- (1) halo,
(2) C₁-alkoxy,
(3) C₁-alkylthio,
(4) CN,
(5) CF₃,
(6) C₁-alkyl,
(7) N₃,
(8) -C(R⁵)(R⁶)-OH,

R³ is hydrogen, C₁-alkyl, CH₂OR⁷, CN, CH₂CN, or C₁-fluoroalkyl,
F, CONR⁷₂;
R⁴ is

- (a) C₁-alkoxy,
(b) C₁-alkylthio,
(c) -OH,
(d) -OCOR⁷,
(e) -SH,
(f) -SCOR⁷,
(g) -OCO₂R⁸,

3 0

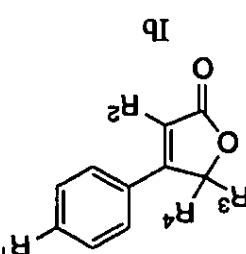
2 5

2 0

1 5

1 0

5

- (h) $-\text{SCO}_2\text{R}_8$,
 (i) OCONR_7^2 , and
 (j) SCONR_7^2 ;
 each R_5 or R_6 is independently selected from the group consisting of
 (a) hydrogen, and
 (b) C1-4alkyl,
 each R_7 is independently selected from the group consisting of
 (a) hydrogen and
 (b) R_8 ;
 each R_8 is independently selected from the group consisting of
 (a) C1-4alkyl,
 (b) phenyl or monosubstituted phenyl wherein the substituents
 may be halo, C1-4alkyl, C1-alkoxy, C1-alkylthio, CN, or
 CF_3 .
 15
 8. A compound according to Claim 7 of formula Ib

 Ib
 20
 R1 is selected from the group consisting of
 (a) $\text{S(O)}_2\text{CH}_3$,
 (b) $\text{S(O)}_2\text{NH}_2$,
 R2 is selected from the group consisting of
 unsubstituted or mono-, di- or tri-substituted phenyl
 wherein the substituent is selected from the group
 consisting of
 (1) halo,
 (2) C1-3alkoxy,
 (3) CF_3 ,
 (4) C1-3alkyl,
 30
 25

- 90 -

R³ is hydrogen, C₁-3alkyl, CH₂OR⁷, C₁-4fluoroalkyl, F, CONR⁷₂;
R⁴ is

- | | | |
|----|---|--|
| 5 | (a) C ₁ -3alkoxy,
(b) C ₁ -3alkylthio,
(c) -OH,
(d) -OCOR ⁷ ,
(e) -SCOR ⁷ ,
(f) OCONR ⁷ ₂ , and
(g) SCONR ⁷ ₂ ; | each R ⁵ or R ⁶ is independently selected from the group consisting of |
| 10 | (a) hydrogen, and
(b) C ₁ -3alkyl, | each R ⁷ is independently selected from the group consisting of |
| 15 | (a) hydrogen and
(b) R ⁸ ; | each R ⁸ is C ₁ -3alkyl. |

9. A compound according to Claim 3

wherein:

2 0 Y is selected from the group consisting of

(a) C(R¹)(R¹²),

(b) oxygen,

(c) sulfur,

R¹ is selected from the group consisting of

2 5

(a) S(O)₂CH₃,

(b) S(O)₂NH₂,

(c) S(O)₂NHC(O)CF₃,

(d) S(O)(NH)NH₂,

(e) S(O)(NH)NHC(O)CF₃,

3 0

(f) P(O)(CH₃)NH₂,

R² is selected from the group consisting of

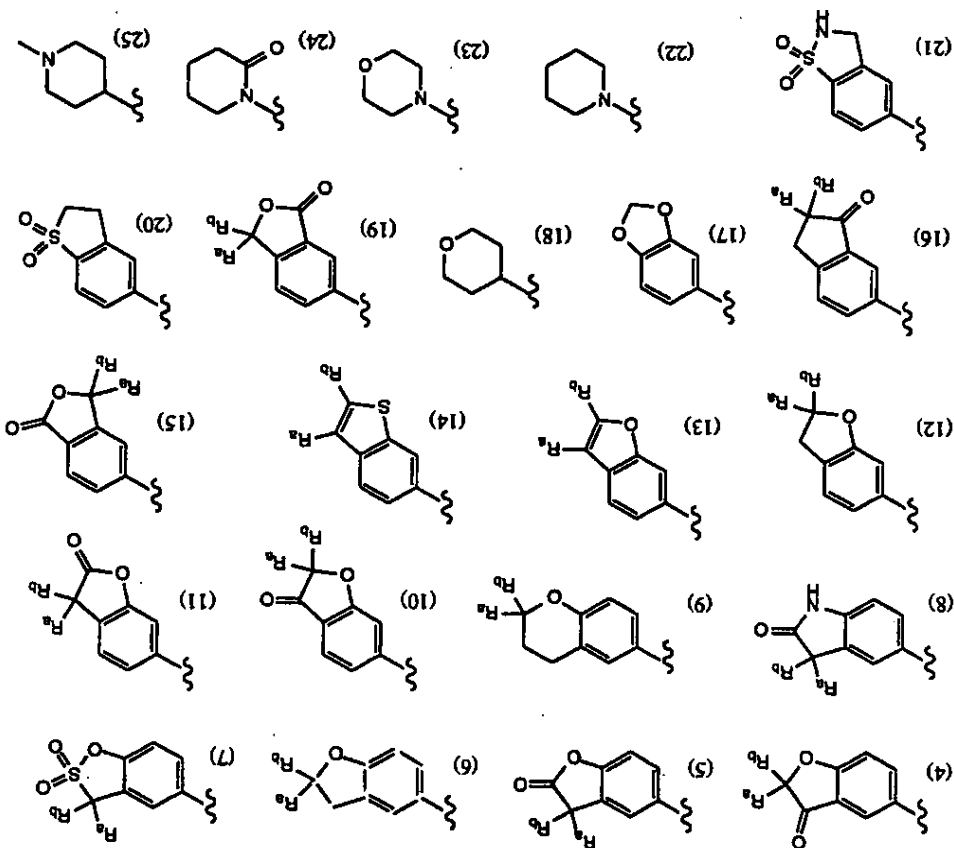
(a)

mono- or di-substituted heteroaryl selected from the group consisting of

- 91 -

(1) furanyl, (2) diaziny], triaziny] and tetraziny], (3) imidazolyl, (4) isooxazolyl, (5) isothiazolyl, (6) oxadiazolyl, (7) oxazolyl, (8) pyrazolyl, (9) pyrrolyl, (10) thiadiazolyl, (11) thiazolyl, (12) thienyl, (13) triazolyl, and (14) tetrazolyl,	5	
	10	
wherein said substituents are selected from the group consisting of	15	
(1) hydrogen, (2) fluoro, chloro, bromo and iodo, (3) C1-alkyl, (4) C1-alkoxy, (5) C1-alkylthio, (6) CN, (7) CF ₃ , (8) N ₃ , (9) -C(R ₅)(R ₆)-OH, and (10) -C(R ₅)(R ₆)-O-C1-alkyl;	20	
(b) a mono- or di-substituted benzoheterocycle, benzocarbocycle or heterocycloalkyl selected from the group consisting of	25	
(1) 2-indolyl, (2) 3-indolyl, (3) 1-methyl-5-indolyl (4) 2-benzofuranyl, (5) 3-benzofuranyl, (6) 5-benzofuranyl,	30	

(7) 6-benzofuranyl,
 (8) 2-benzothienyl,
 (9) 3-benzothienyl,
 (10) 5-benzothienyl,
 (11) 6-benzothienyl,



in which the substituents comprise R_a and R_b and said substituents are selected from halo, -OH, CF_3 , C1-3alkoxy,

C1-3alkylthio, and C1-3alkyl;

R^3 is hydrogen, C1-6alkyl, CH_2OR^7 , CN, CH_2CN , or C1-6fluoroalkyl, F, CONR⁷2, unsubstituted or mono- or di-substituted phenyl, unsubstituted or mono- or di-substituted benzyl, unsubstituted or mono- or di-substituted heteroaryl, unsubstituted or mono- or di-substituted

- 93 -

heteroaryl)methyl, wherein the substituents are selected from the group consisting of

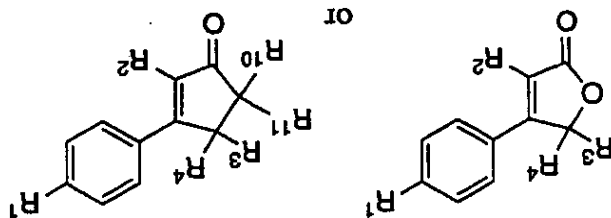
- | | | |
|----|--|-------------------|
| 5 | (1) halo, | |
| | (2) C1-alkyl, | |
| | (3) C1-alkoxy, | |
| | (4) C1-alkylthio, | |
| | (5) CN, | |
| | (6) CF ₃ , | |
| | (7) N ₃ , | |
| 10 | (8) -C(R ₅)(R ₆)-OH, and | |
| | (9) -C(R ₅)(R ₆)-O-C1-10alkyl; | |
| | | R ⁴ is |
| 15 | (a) C1-alkoxy, | |
| | (b) C1-alkylthio, | |
| | (c) -OH, | |
| | (d) -OCOR ⁷ , | |
| | (e) -SH, | |
| | (f) -SCOR ⁷ , | |
| | (g) -OCO ₂ R ⁸ , | |
| 20 | (h) -SCO ₂ R ⁸ , | |
| | (i) OCONR ⁷ ₂ , and | |
| | (j) SCONR ⁷ ₂ ; | |

- | | | |
|----|--|--|
| 25 | each R ⁵ or R ⁶ is independently selected from the group consisting of | |
| | (a) hydrogen, and | |
| | (b) C1-alkyl, | |
| | each R ⁷ is independently selected from the group consisting of | |
| | (a) hydrogen and | |
| | (b) R ⁸ ; | |
| 30 | each R ⁸ is independently selected from the group consisting of | |

- | | | |
|--|---|--|
| | (a) C1-6alkyl, | |
| | (b) phenyl or monosubstituted phenyl wherein the substituents | |
| | may be halo, C1-alkyl, C1-alkoxy, C1-alkylthio, CN, or | |
| | CF ₃ , | |

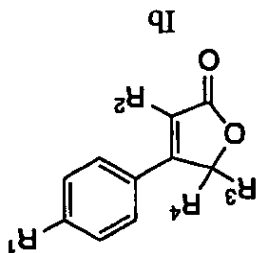
- (c) benzyl or monosubstituted benzyl wherein the substituents may be halo, C1-4alkyl, C1-4alkoxy, CN, or CF₃;
 R¹¹ and R¹² are independently selected from the group consisting of:
 (a) hydrogen,
 (b) C1-10alkyl, CH₂OR⁷, CN, CH₂CN, C1-10fluoroalkyl, F or CONR⁷₂.

10. A compound according to Claim 8 of formula Ib or



or a pharmaceutically acceptable salt thereof.

11. A compound according to Claim 10 of formula Ib



wherein R² is a mono or di substituted heteroaryl wherein heteroaryl is selected from the group consisting of

- (1) furanyl,
 (2) diaziny, triaziny, tetraziny,
 (3) imidazoly,
 (4) isooxazoly,

- 95 -

(5)	isothiazolyl,	
(6)	oxadiazolyl,	
(7)	oxazolyl,	
(8)	pyrazolyl,	
(9)	pyrrolyl,	5
(10)	thiadiazolyl,	
(11)	thiazolyl,	
(12)	thienyl,	
(13)	triazolyl, and	
(14)	tetrazolyl,	10
wherein the substituents are selected from the group consisting of		
(1)	hydrogen,	
(2)	fluoro or chloro,	
(3)	C1-3alkoxy,	15
(4)	C1-6alkylthio,	
(5)	CN,	
(6)	CF ₃ ,	
(7)	C1-3alkyl,	
(8)	-C(R ⁵)(R ⁶)-OH;	20
(9)	-C(R ⁵)(R ⁶)-O-C1-4alkyl.	
12. A compound according to Claim 11 wherein R ² is a mono or di substituted heteroaryl wherein heteroaryl is selected from the group consisting of		
(1)	2-furanyl,	25
(2)	3-furanyl,	
(3)	2-thienyl,	
(4)	3-thienyl,	
(5)	3-isoxazolyl,	30
(6)	4-isoxazolyl,	
(7)	5-isoxazolyl,	
(8)	3-isothiazolyl,	
(9)	4-isothiazolyl,	

- 96 -

13. A compound according to Claim 12 wherein

(10)	5-isothiazolyl,	
(11)	2-oxazolyl,	
(12)	4-oxazolyl,	
(13)	5-oxazolyl,	
(14)	2-thiazolyl,	5
(15)	4-thiazolyl,	
(16)	5-thiazolyl,	
(17)	1,2,3-thiadiazol-4-yl,	
(18)	1,2,3-thiadiazol-5-yl,	
(19)	1,2,4-thiadiazol-3-yl,	10
(20)	1,2,4-thiadiazol-5-yl,	
(21)	1,3,4-thiadiazol-2-yl,	
(22)	1,2,5-thiadiazol-3-yl,	
(23)	1,2,3-oxadiazol-4-yl,	
(24)	1,2,3-oxadiazol-5-yl,	15
(25)	1,2,4-oxadiazol-3-yl,	
(26)	1,2,4-oxadiazol-5-yl,	
(27)	1,3,4-oxadiazol-2-yl,	
(28)	1,2,5-oxadiazol-3-yl,	
(29)	pyrazol-4-yl,	20
(30)	pyrazol-5-yl,	
(31)	1,2,3-triadiazol-4-yl,	
(32)	1,2,3-triadiazol-5-yl,	
(33)	1,2,4-triadiazol-3-yl,	
(34)	1,2,4-triadiazol-5-yl,	25
(35)	1,2-diazinyl,	
(36)	1,3-diazinyl,	
(37)	1,4-diazinyl,	
(38)	1,2,3,4-tetrazin-5-yl,	
(39)	1,2,4,5-tetrazin-4-yl,	30
(40)	1,3,4,5-tetrazin-2-yl, and	
(41)	1,2,3,5-tetrazin-4-yl.	

- 97 -

R² is a mono or di substituted heteroaryl wherein heteroaryl is selected from the group consisting of

- | | | |
|------|------------------------|----|
| (1) | 3-isoxazolyl, | |
| (2) | 4-isoxazolyl, | |
| (3) | 5-isoxazolyl, | 5 |
| (4) | 3-isothiazolyl, | |
| (5) | 4-isothiazolyl, | |
| (6) | 5-isothiazolyl, | |
| (7) | 2-oxazolyl, | |
| (8) | 4-oxazolyl, | 10 |
| (9) | 5-oxazolyl, | |
| (10) | 2-thiazolyl, | |
| (11) | 4-thiazolyl, | |
| (12) | 5-thiazolyl, | |
| (13) | 1,2,3-thiadiazol-4-yl, | 15 |
| (14) | 1,2,3-thiadiazol-5-yl, | |
| (15) | 1,2,4-thiadiazol-3-yl, | |
| (16) | 1,2,4-thiadiazol-5-yl, | |
| (17) | 1,3,4-thiadiazol-2-yl, | |
| (18) | 1,2,5-thiadiazol-3-yl, | 20 |
| (19) | 1,2,3-oxadiazol-4-yl, | |
| (20) | 1,2,3-oxadiazol-5-yl, | |
| (21) | 1,2,4-oxadiazol-3-yl, | |
| (22) | 1,2,4-oxadiazol-5-yl, | |
| (23) | 1,3,4-oxadiazol-2-yl, | 25 |
| (24) | 1,2,5-oxadiazol-3-yl, | |
| (25) | 1,2-diazinyl, | |
| (26) | 1,3-diazinyl, and | |
| (27) | 1,4-diazinyl, | 30 |

14. A compound according to Claim 13 wherein the heteroaryl is selected from the group consisting of

- (1) 3-isothiazolyl,
(2) 4-isothiazolyl,

- 99 -

- (b) R₈ is independently selected from the group consisting of
- (a) C₁-alkyl,
- (b) phenyl or monosubstituted phenyl wherein the substituents may be halo, C₁-alkyl, C₁-alkoxy, C₁-alkylthio, CN, or CF₃.
15. A compound according to Claim 14 wherein the heteroaryl is selected from the group consisting of
- (1) 3-isothiazolyl,
- (2) 4-isothiazolyl,
- (3) 5-isothiazolyl,
- (4) 2-oxazolyl,
- (5) 4-oxazolyl,
- (6) 5-oxazolyl,
- (7) 2-thiazolyl,
- (8) 4-thiazolyl,
- (9) 5-thiazolyl,
- (10) 1,2-diazinyl,
- (11) 1,3-diazinyl, and
- (12) 1,4-diazinyl, and
- wherein the substituents are selected from the group consisting of
- (1) hydrogen,
- (2) fluoro or chloro,
- (3) C₁-alkoxy,
- (4) C₁-alkylthio,
- (5) CN,
- (6) C₁-alkyl, and
- (7) -C(R⁵)(R⁶)-OH,
- 30 R³ is C₁-alkyl, CH₂OR⁷, C₁-fluoroalkyl, F, CONR⁷2; R⁴ is
- (a) C₁-alkoxy,
- (b) C₁-alkylthio,
- (c) -OH,

- 100 -

- (d) -OCOR⁷,
(e) -SCOR⁷;
each R⁵ or R⁶ is independently selected from the group consisting of
(a) hydrogen, and
(b) C₁-3alkyl,
each R⁷ is independently selected from the group consisting of
(a) hydrogen and
(b) R⁸;
each R⁸ is C₁-3alkyl.

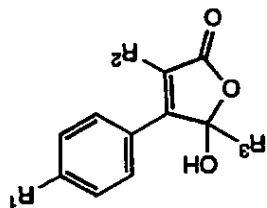
16. A compound according to claim 1 selected from the group consisting of

- 1 5 (1) Benzoic acid, 3-(4-(methylsulfonyl)phenyl)-5-oxo-4-phenyl-2,5-dihydrofuran-2-yl ester,
(2) 5-Hydroxy-4-(4-(methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone,
(3) 5-Hydroxy-3-(3,4-difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,
(4) 5-Hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone,
2 0 (5) 3-(4-Fluorophenyl)-5-hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,
(6) 3-(4-Chlorophenyl)-5-hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,
(7) 3-(3,4-Difluorophenyl)-5-hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,
2 5 (8) 3-(3-Fluorophenyl)-5-hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,
(9) 3-(3,5-Difluorophenyl)-5-hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,
3 0 (10) 5-Methoxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone,
(11) 3-(4-Chlorophenyl)-5-methoxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,

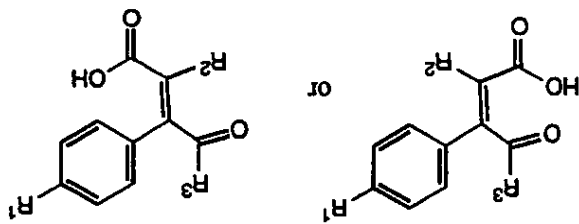
(12) 3-(3,4-Difluorophenyl)-5-methoxy-5-methyl-4-(4-methylsulfonyl)phenyl-2-(5H)-furanone,	
(13) 3-(3-Fluorophenyl)-5-methoxy-5-methyl-4-(4-methylsulfonyl)phenyl-2-(5H)-furanone,	
(14) 3-(3,5-Difluorophenyl)-5-methoxy-5-methyl-4-(4-methylsulfonyl)phenyl-2-(5H)-furanone,	5
(15) 3-(4-Fluorophenyl)-5-methoxy-5-methyl-4-(4-methylsulfonyl)phenyl-2-(5H)-furanone,	
(16) 5-Ethoxy-3-(4-Fluorophenyl)-5-methyl-4-(4-methylsulfonyl)phenyl-2-(5H)-furanone,	
(17) 3-(4-Fluorophenyl)-5-methyl-4-(4-methylsulfonyl)phenyl-2-(5H)-furanone,	10
(18) 3-(4-Fluorophenyl)-5-isopropoxy-5-methyl-4-(4-methylsulfonyl)phenyl-2-(5H)-furanone,	
(19) 5-Methyl-5-methylthio-4-(4-methylsulfonyl)phenyl-3-phenyl-2-(5H)-furanone,	15
(20) 5-Ethylthio-5-methyl-4-(4-methylsulfonyl)phenyl-3-phenyl-2-(5H)-furanone,	
(21) 5-Ethyl-5-hydroxy-4-(4-methylsulfonyl)phenyl-3-phenyl-2-(5H)-furanone,	
(22) 5-Ethyl-3-(3-Fluorophenyl)-5-hydroxy-4-(4-methylsulfonyl)phenyl-2-(5H)-furanone, and	20
(23) Acetic acid, 3-(4-(methanesulfonyl)phenyl)-5-methyl-5-oxo-4-phenyl-2,5-dihydrofuran-2-yl ester	
(24) 5-Hydroxy-5-methyl-4-(4-methylsulfonyl)phenyl-3-(2-naphthyl)-2-(5H)-furanone,	25
(25) Sodium 2-(4-Fluorophenyl)-3-((4-methylsulfonyl)phenyl)-4-oxo-2-pentenoate, and	
(26) Sodium 2-(4-chlorophenyl)-3-((4-methylsulfonyl)phenyl)-4-oxo-2-pentenoate.	30

17. A pharmaceutical composition for treating an inflammatory disease susceptible to treatment with a non-steroidal anti-inflammatory agent comprising:

- 3 0 22. A compound according to Claim 1 of formula
- therapeutically effective amount of a compound according to Claim 1 and a pharmaceutically acceptable carrier.
- 2 5 21. A method of treating inflammation in a patient for which non-steroidal antiinflammatory drugs may be contra-indicated comprising:
- 2 0 20. A method of treating cyclooxygenase mediated diseases advantageously treated by an active agent that selectively inhibits COX-2 in preference to COX-1 comprising:
- 1 5 19. A method of treating an inflammatory disease susceptible to treatment with an non-steroidal anti-inflammatory agent comprising:
- 1 0 18. A pharmaceutical composition for treating cyclooxy- genase mediated diseases advantageously treated by an active agent that selectively inhibits COX-2 in preference to COX-1 comprising: a non-toxic therapeutically effective amount of a compound according to Claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16, and a pharmaceutically acceptable carrier.
- 5 a non-toxic therapeutically effective amount of a compound according to Claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16, and a pharmaceutically acceptable carrier.

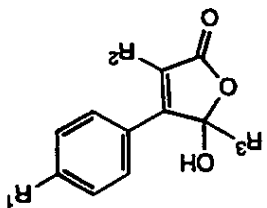


or tautomer thereof, which is

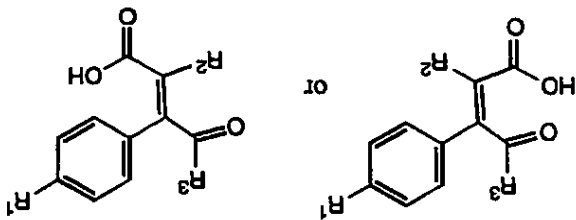


5

23. A compound according to Claim 7 of formula



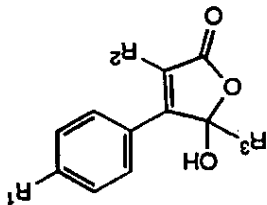
or tautomer thereof, which is



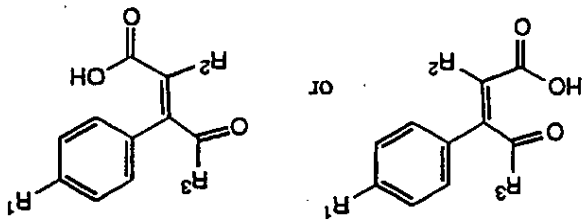
10

24. A compound according to Claim 8 of formula

- 104 -



or tautomer thereof, which is



or

25. A pharmaceutically acceptable salt of a compound of formula (I), as defined in claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 22, 23 or 24.

26. A non-steroidal anti-inflammatory pharmaceutical composition comprising an acceptable, anti-inflammatory amount of a compound of formula (I), as defined in claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 17, 22, 23 or 24, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

27. A COX-2 selective inhibitor pharmaceutical composition comprising an acceptable COX-2 selectively inhibiting amount of a compound of formula (I), as defined in claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 22, 23 or 24, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

28. A compound of formula (I), as defined in claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 22, 23 or 24, or a pharmaceutically acceptable salt thereof, for use in treating inflammation in a patient for which non-steroidal anti-inflammatory drugs may be contra-indicated. 5
29. Use of a compound of formula (I), as defined in claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 22, 23 or 24, or a pharmaceutically acceptable salt thereof, for use in the manufacture of a medicament for treating cyclooxygenase mediated diseases advantageously treated by an active agent that selectively inhibits COX-2 in preference to COX-1. 10
30. Use of a compound of formula (I), as defined in claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 22, 23 or 24, or a pharmaceutically acceptable salt thereof, as an anti-inflammatory agent. 15
31. Use of a compound of formula (I), as defined in claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 22, 23 or 24, or a pharmaceutically acceptable salt thereof, as a selective inhibitor of COX-2. 2.

INTERNATIONAL SEARCH REPORT

Int. Application No
PC/CA 96/00306

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D307/60 A61K31/22 A61K31/38 A61K31/34 A61K31/365
A61K31/41 C07D307/64 C07D405/04 C07D407/04 C07D409/04
C07D417/44 C07C317/44
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
----------	--	-----------------------

X	WO A,95 00501 (MERCK FROSST CANADA INC DUCHARME YVES (CA); GAUTHIER JACQUES YVES) 5 January 1995 cited in the application see abstract; claims; examples 12,56-60; table III see page 72, line 20 - line 25; table II see page 73, line 15 - line 22; table II --- US, A,5 474 995 (DUCHARME YVES ET AL) 12 December 1995 cited in the application see abstract; claims 1,18-25; examples 13,56-60 -----	1-31
P, A		1-31

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "B" earlier document published on or after the international filing date
- "C" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "D" document referring to an oral disclosure, use, exhibition or other means
- "E" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "Z" document member of the same patent family

Date of the actual completion of the international search

16 August 1996

Date of mailing of the international search report

23.08.96

Authorized officer

Paissdor, B

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA96/00306

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely: Remark: Although claims 19-21 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/com-position.
2. ☐ Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Inv
onal Application No
PC1/CA 96/00306

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
---	---------------------	----------------------------	---------------------

WO-A-9500501	05-01-95	US-A- AU-B- AU-B- BR-A- CA-A- CA-A- CA-A- CA-A- CA-A- CA-A- WO-A- EP-A- FI-A- NO-A- NO-A- PL-A- US-A- ZA-A-	5474995 1269495 6967494 9406979 2163888 2176973 2176974 9518799 0705254 956119 955256 960393 312196 5536752 9404501	12-12-95 01-08-95 17-01-95 05-03-96 05-01-95 25-12-94 25-12-94 13-07-95 10-04-96 19-12-95 23-02-96 09-07-96 01-04-96 16-07-96 13-03-95
--------------	----------	--	---	--

US-A-5474995	12-12-95	AU-B- AU-B- BR-A- CA-A- CA-A- CA-A- CA-A- CA-A- WO-A- WO-A- EP-A- FI-A- NO-A- NO-A- PL-A- US-A- ZA-A-	1269495 6967494 9406979 2163888 2176973 2176974 9500501 9518799 0705254 956119 955256 960393 312196 5536752 9404501	01-08-95 17-01-95 05-03-96 05-01-95 25-12-94 25-12-94 05-01-95 13-07-95 10-04-96 19-12-95 23-02-96 09-07-96 01-04-96 16-07-96 13-03-95
--------------	----------	---	---	--